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MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

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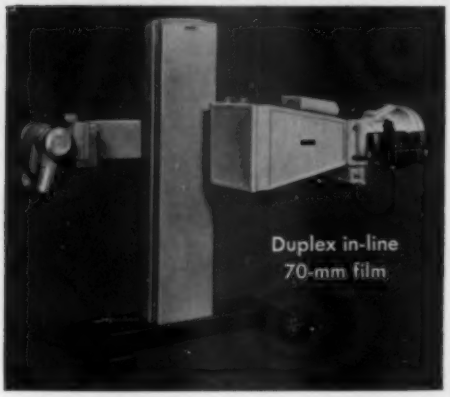

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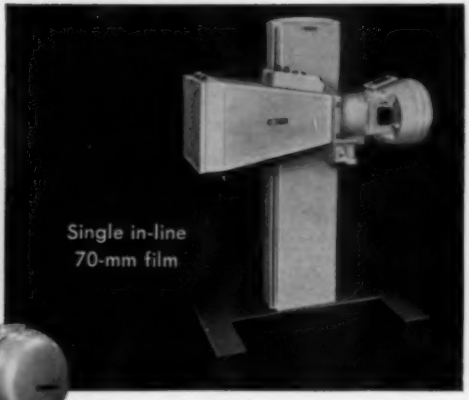

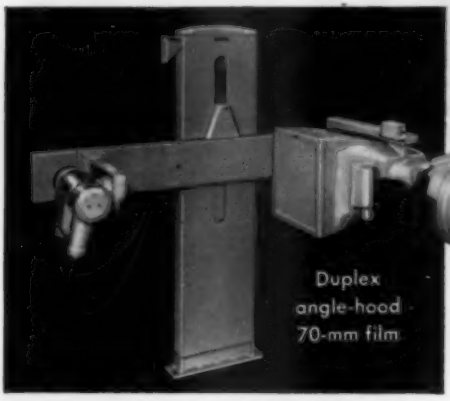

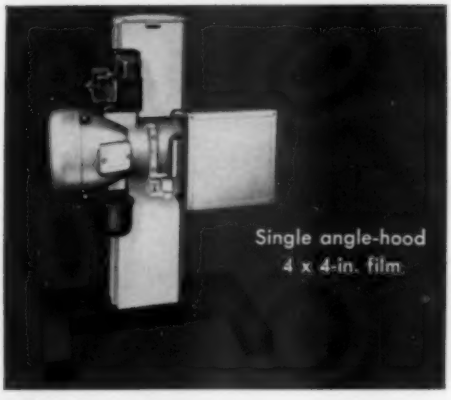

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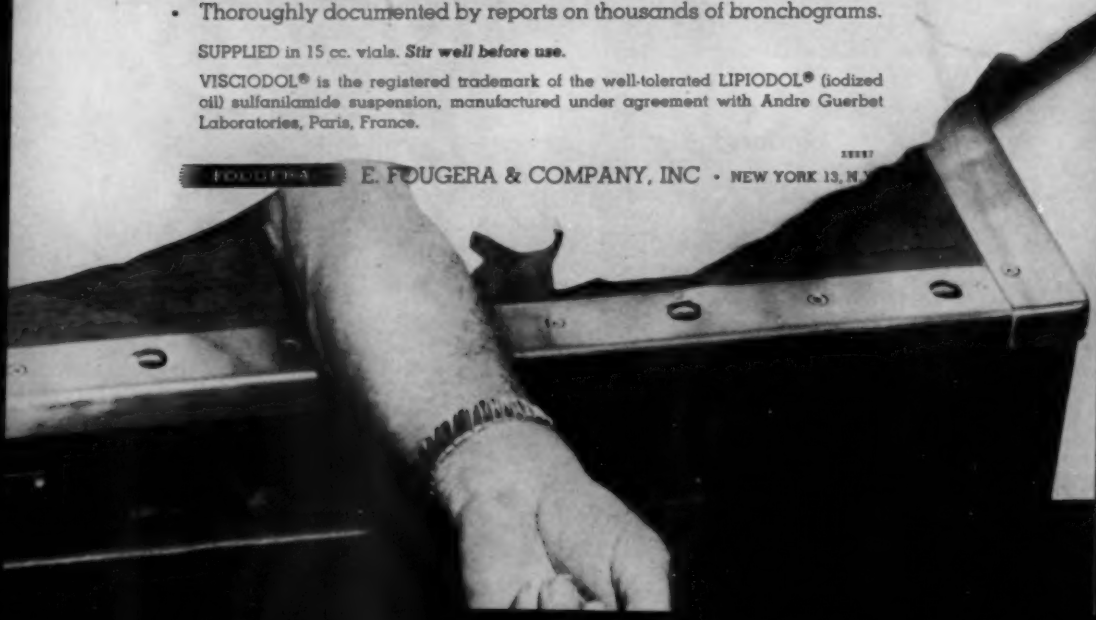

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1. Molthan, L., Cohen, R.V., and Zarafonetis, C.J.D.: Am. Rev. Tuber. *71*:220, 1955.
2. Cohen, R.V., Molthan, L., and Zarafonetis, C.J.D.: Dis. Chest *30*:418, 1956.

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1. DeBakey, M. E., Cooley, D. A., Morris, G. C. Jr., Collins, H.: Arteriovenous Fistula Involving the Abdominal Aorta, Annals of Surgery, *147:* 646 (May, 1958)

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THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES

VOLUME 78 *September, 1958* NUMBER 3

A SCHEMA FOR TUBERCULOSIS REVISITED[1,2]

WILLIAM B. TUCKER

(Received for publication May 16, 1958)

Three years ago this month, at the 1955 annual meeting of the North Carolina Trudeau Society in Durham, Dr. Carl Muschenheim of New York presented before this society a scholarly and provocative dissertation entitled "A Schema of Treatment in Tuberculosis."[3] In it one of our closest students in the field of tuberculosis gave this group, of which I was then privileged to be a member, the benefit of his balanced perspective—a difficult navigational feat among the eddies and currents of facts and half-established truths in the ever-changing seascape of phthisiology.

Dr. Muschenheim correctly pointed out the limitations of large-scale controlled trials, and the advisability, even the necessity, for the individual physician not to rely too greatly on interpretations derived from such studies, and to retain his clinical initiative in his therapeutic approach to the individual patient. More importantly, Dr. Muschenheim outlined a rational basis for individualizing therapy according to a number of the important variables which are of everyday concern to every physician called upon to treat tuberculous patients.

Your program committee has done me the great honor to suggest as the title for my comments this evening the subject—"Remarks." I propose to take advantage of this opportunity, unparalleled in my personal experience, and "remark" on many of the thoughts and ideas I have had on tuberculosis and its clinical management from time to time. A slightly more descriptive title for my "Remarks" this evening might be "A Schema for Tuberculosis Revisited."

* * *

Having had the opportunity to participate in a cooperative study, that of the Veterans Administration and Armed Forces, in the chemotherapy of tuberculosis, you will not be surprised if I turn my attention first to the question of such cooperative studies and their contributions.

May I say at once that such large-scale studies are no panacea, no final answer

[1] From the Tuberculosis Service, Veterans Administration, Washington, D. C.

[2] Presented before the annual meeting of the North Carolina Trudeau Society, Wilmington, North Carolina, April 25, 1958.

[3] Am. Rev. Tuberc., 1955, *72*, 1.

to any clinical problem. In fact they play a relatively minor role in clinical medicine. They are entirely dependent in the first instance on observations of individual students of medicine for the definition and delineation of a question to be posed, and of the answer to be sought. So-called cooperative studies are to be regarded as supplementary to the more common so-called "empirical" method, that of the close student of medical variables. In the best and truest sense, cooperative and individual medical studies are mutually complementary, the one contributing to the other.

There is no particular magic in cooperative studies. Their advantage lies in a uniform approach to a diversified problem; an opportunity to assemble data more rapidly than on an individual basis, and thus perhaps to arrive at a meaningful answer sooner. The customary cooperative study, as developed in the past decade or so, is designed to answer a limited number of questions. Ideally, a study attempts to answer only one question at a time, such as the difference between one dose of a drug and another; between one drug and another; between a certain procedure and the result without that procedure, et cetera. If such a study is well designed and properly carried out, the answer may be accepted with a considerable degree of confidence as to the influence of the one variable under study for the particular set of conditions in that study, and that is all. We in the Veterans Administration have been concerned, as results of our studies have been subject to extrapolated interpretation—to apply to conditions not within the limits of the investigation. Dr. Muschenheim three years ago was quite rightly critical, I think, of this tendency.

This comment does not reflect any sudden change in confidence on my part in cooperative studies. Quite the contrary: I do believe that they have established a firm place for themselves in American medicine, as attested by more than 20 cooperative studies currently in progress in the Veterans Administration in such diverse fields as atherosclerosis, tranquilizing drugs, histoplasmosis, antihypertensive drugs, esophageal varices, coccidioidomycosis, solitary pulmonary nodules, multiple sclerosis, and certain malignancies, and by an increasing number of other cooperative studies. But the limitations to their contributions need to be clearly recognized.

May I also make a distinction between "cooperative" studies and "controlled" studies. Because most cooperative studies have the principle of scientific controls built into them, there often is confusion between two quite different techniques. Cooperative studies may or may not incorporate controls; the principle of controls may quite as readily be introduced into the individual as into the cooperative investigation.

Let us now do a little mental arithmetic. It is often stated that "no two cases (of any disease) are alike"; yet we of necessity must seek as many common denominators as seem to be readily available and classify according to certain measurable variables. The clinical problem with fewer variables is obviously easier to study; that with many, much more difficult. Tuberculosis is clearly one of the latter. Suppose that with regard to all variables considered to be important in the treatment of tuberculosis a classification could be as simple

as "black or white," "yes or no," with no shades in between: for example, male or female; white or non-white; under forty years of age (or 50 or any other age) or over 40; with cavity or without; with unilateral pulmonary involvement or bilateral; with previous treatment or without; et cetera, et cetera. Mathematics tells us that according to the number of such variables so *di*chotomized, n, the number of groups possible is represented by the simple formula 2^n. If there are two variables, e.g., sex and color, there are 2^2, or 4, possible groups; if three variables—adding age under or over 40—2^3, or 8; and if a minimum of 8 variables is reasonably selected, according to our clinical beliefs or prejudices, the answer as to the number of subgroups is 2^8, or 256. (If classification were based on trichotomies instead, 3^8 would come to 6,561.) This means that, if a particular answer to a particular study is sought in every possible subgroup, the total number of patients to be included in a study would need to be tremendous, for each subgroup's analysis to have statistical validity. The literal impossibility of accurately studying the effect of a therapeutic variable in every subgroup, however, should not deter us from making a start, and this has been done. It is now possible to say, for example, that certain combinations of drugs are approximately equally effective in noncavernous pulmonary tuberculosis, but are not therapeutically equivalent for more advanced disease. But as more evidence is carefully collected, much more of this subgroup analysis needs to be done.

It has been repeatedly stated that the field of tuberculosis is rapidly changing. This rate of change, however, I think has slowed down a little in recent years, as compared with the late 1940's and early 1950's. Three years ago Dr. Muschenheim said, "We cannot wait for the results of long-term follow-up studies now in progress, which may and probably will determine which of the currently available methods is the best in each type and variety of case. By the time these answers are forthcoming, more likely than not there will be new developments which will cause the best of present methods to be outmoded." This applies to 1958 as well as to 1955, but perhaps we have "plateaued" a bit and can pause a little more leisurely in 1958 to see what has been accomplished.

Much as I admire the astute clinician who arrives at a sound evaluation of the many variables in clinical medicine, I would be remiss if I did not remind you of the ever-present possibility of error in the empirical clinical method. Beecher, of Boston, has said, with regard to establishing the proper dose of morphine for the control of pain in carefully controlled studies that "the tedious conditions (of a controlled study) . . . permit accurate results to be arrived at more rapidly than is true of the old-fashioned method of . . . trial and error, arriving in decades or centuries at an approximation of the truth."

* * *

Having now luxuriated for some fifteen minutes in expressing some philosophic thoughts on what might be called "science in medicine," may I turn to some concrete questions in the therapy of pulmonary tuberculosis which are still very much with us.

Is there a single "drug of choice"? We know that no drug is better than tuber-

culostatic; yet I believe that today, in contrast with 1955, there is little debate but that isoniazid is the single most effective drug in the treatment of tuberculosis. This assertion cannot be completely documented but does have increasingly unanimous support. It does not mean, however, that other drugs do not approach isoniazid in efficacy or that it is unethical to treat at least some kinds of cases of tuberculosis with drugs other than isoniazid. But I believe it is proper to emphasize that isoniazid *is* the drug of first choice.

Does *single* drug therapy, with isoniazid alone, have a place in the treatment of tuberculosis? Most emphatically, yes. The Cornell-New York Hospital group has done yeoman service for all of us in keeping alive this thought, often I am sure, representing a minority viewpoint. The widely held view that multiple-drug therapy is desirable stems of course from the solidly established fact—from large series of cases in cooperative studies—that there is a lower rate of emergence of drug resistance to one drug when another effective agent is administered concomitantly; and the further observation that drug therapy with a specific agent is less effective, if not ineffective, if drug susceptibility is lost (with certain reservations in the case of isoniazid). But what may have been shown for those large series of cases *on the whole* does not necessarily apply to *all* subgroups. Further analysis of data collected by the Veterans Administration in 1952, when isoniazid alone was being compared with two two-drug combinations, showed remarkably little if any difference in effectiveness for minimal and moderately advanced disease. The New York Hospital group has treated more advanced disease with isoniazid alone, with what they regard as satisfactory results in the majority of cases. It is my personal interpretation of their data that their results are not quite as good, for their entire group, as might be expected had another drug been added, either streptomycin or PAS; but the important thing is that in "32 unselected previously untreated advanced cases" completely satisfactory results were obtained in 66 per cent. And Dr. Phillips, at our Chemotherapy Conference in Memphis last February, reported in a study of 150 cases of noncavernous pulmonary tuberculosis randomly allocated to isoniazid alone or to isoniazid and PAS that results were very nearly identical for the two groups.

These are the relatively few *facts* about the use of isoniazid alone. But we may be permitted on the basis of them and other data to speculate beyond them. May there not be a point, after an initial period of two-drug therapy (if such is indicated), when it may be entirely appropriate to change to a continuation of therapy with isoniazid alone? And is it not appropriate for many more minimal tuberculous conditions, especially those wherein there is not a rapid discharge of tubercle bacilli, and presumably therefore less likelihood of emergence of drug resistance, to treat with isoniazid alone? The evidence available to me suggests that it is.

For cases of pulmonary tuberculosis which are definitely cavernous, however, and especially for those with cavities more than 2.0 cm. in diameter, I believe it is wise to prescribe two antituberculous drugs concomitantly. For just such cases, the drug regimen which was found to be most efficacious before the advent

of isoniazid, intermittent streptomycin and daily PAS, has now been shown definitely to be less effective than either of two isoniazid-containing two-drug regimens, isoniazid-streptomycin or isoniazid-PAS. This is then, for such more advanced cases, to reaffirm the statement that isoniazid is the treatment of choice.

But which of the two drugs generally available, streptomycin or PAS, is to be the companion to isoniazid? This is not an easy question to answer, for it involves ease of administration, cost, patient acceptability, and toxicity as well as efficacy; and at least some of these considerations vary with age, race, geography, and other factors. Clearly, if we had two equally effective two-drug combinations available—or, better yet, still more—this would not be a serious problem. Objection is raised by some to employing both isoniazid and streptomycin on the theory that the two "best" drugs would no longer be in reserve if there is "therapeutic failure." I agree with Dr. Muschenheim that this argument is not to be taken too seriously. In the first place, the combination is highly effective. And in the second, an increasing number of drugs, for various reasons designated as "second-line," are available. Thus, if there is "failure" with isoniazid and streptomycin, pyrazinamide and PAS, viomycin and PAS, and certain other combinations may yet contribute much, for PAS is an effective antagonist to drug resistance in combination with many other antituberculous drugs.

In combination with isoniazid, streptomycin may be given daily or intermittently, i.e., every second or third day or twice a week. There is clear evidence that intermittent streptomycin is less effective than daily streptomycin as a companion to daily isoniazid, from the standpoint of emergence of isoniazid resistance, and to a certain extent from the standpoint of the associated phenomenon of "relapse." Having found that intermittent streptomycin as the companion to daily PAS was as effective as daily streptomycin, and thus having employed streptomycin on an intermittent basis for many years, it has been difficult for many physicians—and patients—to accept the possible desirability of again employing streptomycin on a daily administered basis. I believe, however, that, if the decision is to employ streptomycin in combination with isoniazid in the more advanced cases, it is wise to recommend it on a daily basis at least for the first few months of treatment, or until cavities close, sputum "converts," or the disease otherwise approaches reasonable stability, after which it may be changed to intermittent administration. An exception to this may be the elderly patient in whom there is more concern as to eighth-nerve toxicity. However, it has been the experience of some who in recent years have used daily streptomycin extensively that it is widely accepted by most patients, including the more elderly, if there is proper orientation.

The other major possibility of course is to prescribe PAS along with isoniazid, and perhaps this is the drug regimen most widely employed today. Studies in this country and in Great Britain have very adequately demonstrated that this is a highly effective regimen, practically the equivalent of daily isoniazid and daily streptomycin, and more effective than daily isoniazid and intermittent streptomycin.

A word of caution, however. The studies referred to have demonstrated this for *all* cases in the groups under investigation, in a statistical sense; and have tended to show considerable equivalence in the subgroups with less extensive disease. If there is "therapeutic failure" on the combination of isoniazid and PAS, streptomycin is in reserve; and pyrazinamide, viomycin, or cycloserine may be combined with streptomycin; but streptomycin is thought by some to be a less effective antagonist to drug resistance than PAS. On this basis some prefer the initial choice of isoniazid and streptomycin. But I personally believe that this is not the basis for making the decision, and that sufficient other drugs remain in reserve in either instance.

Still another question involving these three drugs, isoniazid, streptomycin, and PAS, is currently controversial. It might be posed as follows: "If two drugs are, for more advanced cases, 'better' than one, why may all three not be 'better' than two?" Most of us have been in this position of uncertainty on this point, particularly in the face of the most serious forms of tuberculosis, in which an "everything to be gained nothing to be lost attitude" may prevail. Yet it is pertinent to examine the evidence.

Aside from many individuals studies, which have shown that even the most serious and emergent forms of tuberculosis respond well to less than "triple-drug therapy," may I present some evidence from a study initiated by the Veterans Administration and Armed Forces in 1955, which compares by random allocation *only for cavitary cases*, isoniazid-PAS, isoniazid-daily-streptomycin, and isoniazid-daily-streptomycin-PAS, presented in February in Memphis by Mrs. Livings.

In figure 1 the results are compared after four months of therapy among moderately advanced cases with respect to roentgenographic improvement and "conversion" of sputum or gastric contents by culture; and in figure 2 the same comparison is made of the same cases after eight months of therapy. Particularly with respect to the more reliable observation of "bacteriologic conversion," there is no difference whatsoever, for moderately advanced cases,

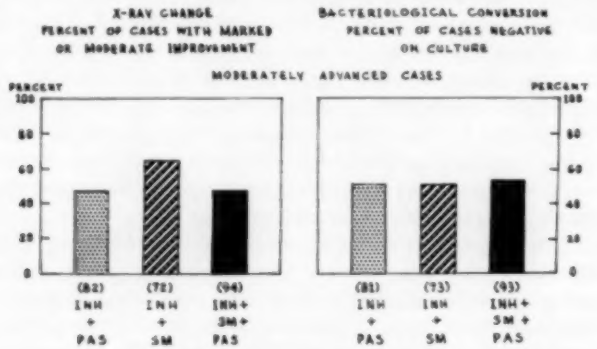

FIG. 1. General regimens: Original treatment of randomized drug-susceptible patients—observations at four months.

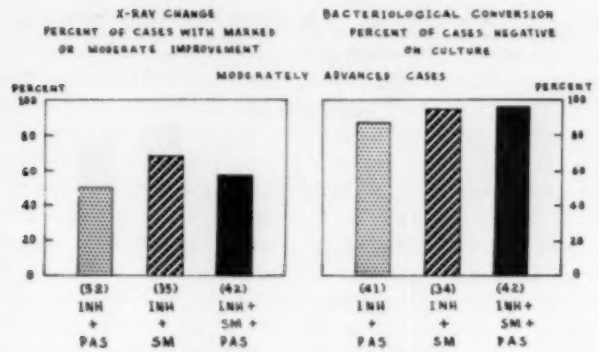

FIG. 2. General regimens: Original treatment of randomized drug-susceptible patients—observations at five to eight months.

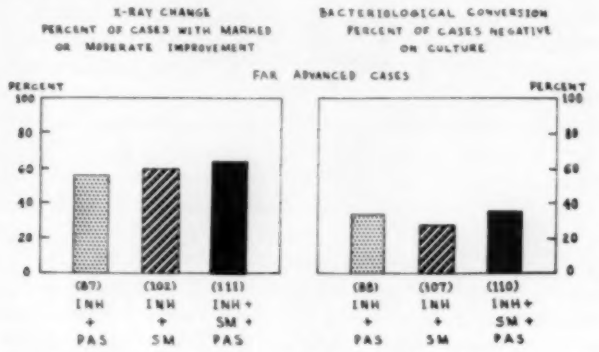

FIG. 3. General regimens: Original treatment of randomized drug-susceptible patients—observations at four months.

among these three regimens. In figure 3 the same comparison is made for far advanced disease at four months; and in figure 4, at eight months. Again there is no significant difference in these measures of therapeutic efficacy. Similar comparability was found with regard to relapse rates and to cavity closure rates. Certainly such data do not suggest that "triple-drug therapy" is superior to either two-drug regimen, even in the most advanced cases. This study is still continuing, and it is possible that further analysis will somewhere uncover the fact that for a limited segment of the pulmonary tuberculosis population all three drugs may actually be indicated; but it is not likely that there is justification for anything like routine employment of all three. And as table 1 indicates, there is considerably more toxicity when all three drugs are employed. These data show that it was necessary to discontinue "triple-drug therapy" in 22 per cent, as contrasted with only 15 per cent of streptomycin-isoniazid patients, and in only 7 per cent of isoniazid-PAS patients.

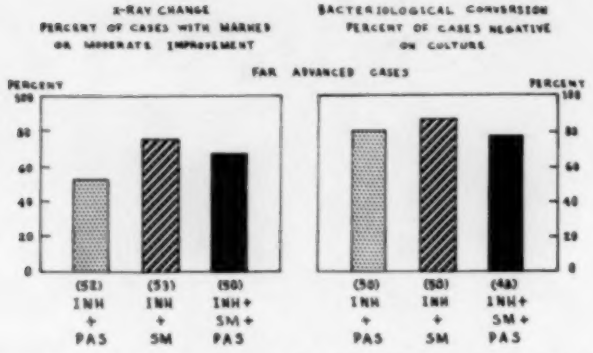

FIG. 4. General regimens: Original treatment of randomized drug-susceptible patients—observations at five to eight months.

TABLE 1

GENERAL REGIMENS

TOXICITY

	Regimen					
	Isoniazid + PAS		Isoniazid + Streptomycin		Isoniazid + Streptomycin + PAS	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Number of patients	192		199		237	
Incidence of toxicity	20	11	43	22	97	41
To isoniazid	1	1	3	2	5	2
To streptomycin	—	—	40	20	54	23
To PAS	19	10	—	—	38	16
Toxicity causing change of drugs	12	7	29	15	51	22
To isoniazid	1	1	3	2	2	1
To streptomycin	—	—	26	13	32	14
To PAS	11	6	—	—	17	7

Still another variable of isoniazid therapy is currently under investigation: that of high doses of isoniazid, by which I shall mean more than the customary dose of about 5 mg. per kg. of body weight. The general subject is familiar to this audience, and I shall not go into detail. The argument, in simple outline, is that a certain relatively small percentage of humans "inactivate" isoniazid metabolically sufficiently rapidly so that "ineffective" concentrations in plasma, and presumably in various body tissues, result; and that the administration of much higher doses of isoniazid or the simultaneous administration of metabolic antagonists to such rapid inactivation, resulting in higher concentrations, assures "effective" levels. The probability is that this phenomenon applies to a relatively small number of patients; but I agree at once that it is important to find out to what extent it does apply, and we are studying this question on a cooperative

basis at the present time. At the moment, particularly for very advanced disease cases, especially if adequate laboratory facilities exist, I should say that it is wise for each patient to find out whether he is a rapid inactivator or not, and then individualize dosage of isoniazid and associated drugs; but I hasten to add that I cannot now estimate with accuracy how large is the percentage of patients to whom this problem may apply.

Another variable of drug therapy which certainly perplexes is that of duration of therapy. And it has not been easy to plan a "scientific" study of this variable. This illustrates a problem of clinical research which deserves especial mention. To wit: when clinical *opinion*—some might call it "prejudice"—suggests that one form of treatment is better than another, it is extremely difficult, for ethical reasons, to assign patients by random allocation to forms of therapy judged to be less effective. As a matter of fact, if such "prejudgment" exists, it is probably better not to attempt such a random allocation study, for bias is very likely indeed to be introduced and to vitiate the results.

Thus it is that to date there has been no satisfactory objective study of duration of therapy. True, at present, investigations of a cooperative nature are under way both in the United States and in Great Britain; but it will be years before this evidence is in hand, and in the meantime we must make decisions.

One of the best approaches to the solution of this question, short of the ideal study, came from an examination of the VA-Armed Forces data from the 1950–1952 period, when streptomycin and PAS were used for varying lengths of time, averaging just short of twelve months. Because duration could be determined by the investigator, according to the requirements of the individual case, it was found clearly that those patients with more advanced disease were, understandably, treated for longer periods of time. It is safe to assume that, if patients with *less* advanced disease, treated for a *shorter* period of time, have results which are *worse* than those patients with *more* advanced disease treated for *longer* periods of time, then longer treatment is "better" than shorter. In figure 5, such a com-

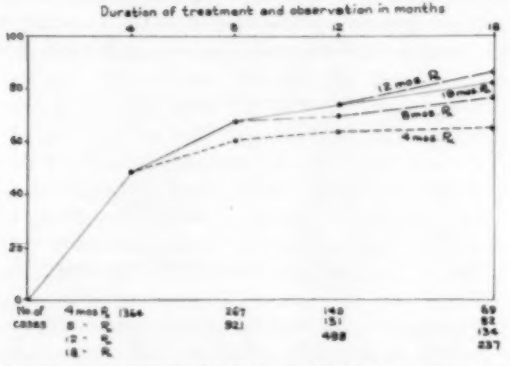

FIG. 5. Effect of duration of antimicrobial therapy (with 3 streptomycin-PAS regimens)—On conversion of sputum (gastric washings) by culture.

parison is made with respect to bacteriologic "conversion"; if therapy is stopped at four months, and observations are made at eight, twelve, and eighteen months, conversion rates are as indicated on the lowest line; this graphically demonstrates that results are "better" bacteriologically with each additional increment of duration of therapy, although with each increment the advantage is less; and results are very similar between twelve and eighteen months. Figure 6, which shows roentgenographic relapse rates, may be interpreted with exactly the same result. The conclusion from such an analysis is that eight months is better than four, twelve better than eight, and eighteen better than twelve; the suggestion is that somewhere between eighteen and twenty-four months the "asymptote" may be reached or very nearly reached. But again this does not answer the question whether this applies to different subgroups of pulmonary tuberculosis. The probability is, I think, that if we had sufficient data, different "optimum" durations would be found for different classes of disease, all the way, perhaps, from a minimum of maybe eight months or so for the "most minimal minimal," possibly to truly "indefinite" duration for the most advanced. These data are only suggestive, and similar analyses should be carried out for isoniazid-containing regimens, and for longer durations, and with longer follow-up observations. Without the complete evidence, however, I believe it is wise to advise a minimum of at least twelve months in all cases, and of eighteen to twenty-four months in nearly all advanced cases.

I have concentrated my attention so far on variables of drug therapy for "original-treatment" pulmonary tuberculosis to the three most commonly employed drugs. Today we have in fact, in addition to these three, pyrazinamide, viomycin, cycloserine, oxytetracycline, the thiosemicarbazone family, the thiocarbanilides, streptovaricin, and now kanamycin, a total of at least 10 quite separate and distinct drugs, of varying effectiveness, toxicity, and usefulness—truly a "plethora" compared to a short dozen years ago. Many reasons exist as to why one of the three commonest drugs may not be appropriate, and others may be indicated. Let me quote another mathematical formula to you. Out of 10 drugs how many two-drug combinations may there be? I am told that the answer is $n(n-2)/2$. If n, then, is 10, the answer is 45. In other words, aside from varia-

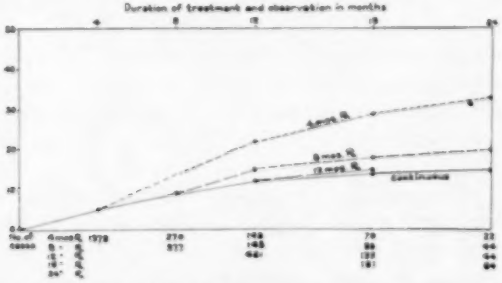

FIG. 6. Effect of duration of antimicrobial therapy (with 3 streptomycin-PAS regimens)—On unfavorable roentgenographic change.

tions of dosage, it is possible to have 45 two-drug combinations from among those listed. And it is surprising how many of these actually have been used and reported upon.

Lest there be concern at this point, let me assure you that I shall not pursue this much further. As a general principle, it is wise to determine drug susceptibility, and administer those drugs to which the organisms are most susceptible (or are likely to be) and in which there is the least likelihood of toxicity. The problems of "re-treatment" after "original drug treatment" has "failed" are endless. But with a stout heart, endless patience, and much persistence and adherence to sound principle, it is quite astonishing what can be accomplished. We in the Veterans Administration may properly be accused of having failed in our obligation properly to study such problems of re-treatment; actually we have tried, without much success. If any of you has a good sound idea in this direction, it will be welcome.

Akin to drug therapy of tuberculosis, in the antimicrobial sense, is the current interest in the role of steroid therapy. A recent report from Scotland is of especial interest. Clearly this question needs to be studied further. I think it is likely that for critically ill patients it can be demonstrated that careful use of the steroids may be life-saving on occasion; much less clear is the picture of the proper place of steroids in the "average," nontoxic patient with active pulmonary tuberculosis. Probably it will be shown that symptomatically, and with regard to such observations as roentgenographic improvement, "conversion" of sputum, cavity closure, et cetera, in the early months of therapy, antimicrobial therapy *with* steroids will be slightly "better" than without; but I doubt very much if the difference will be found to be great or long-lasting; and until more evidence is in, I would certainly not recommend steroid therapy as a routine.

Drug treatment of tuberculosis is fairly new; steroid therapy is even newer. Because these have been with us a relatively short time, conceptions are less well established than in the case of some older forms of therapy of pulmonary tuberculosis. Yet in theory, at least, I think we would all agree that *with* antimicrobials available, our conceptions as to other variables of therapy should be re-examined.

Only one or two small studies of pneumothorax with antimicrobial therapy have been carried out. They suggest that complications of the procedure previously so prevalent and troublesome are far less frequent and serious under the protection of drugs. Yet the fact remains that pneumothorax today is used scarcely at all, unquestionably because without it and all its disadvantages such good results can be obtained. There is less unanimity with respect to pneumoperitoneum. Cooperative studies of this form of collapse, with antituberculous drugs, have to my satisfaction demonstrated that not much is to be gained, but I know that some in the state of North Carolina disagree with me.

There is also a mild renascence of interest in thoracoplasty; and certainly some of its disadvantages prior to the advent of effective drugs are now overcome. But to me thoracoplasty is not primarily a physiologic procedure, is much less "needed" (in the old sense) than formerly, and is esthetically to be decried.

Clearly the antituberculous drug era has made possible the advances in re-

sective surgery for pulmonary tuberculosis with which we are all so familiar. But, in the field of resectional surgery of the lungs, no truly satisfactory study has been carried out on which we may with satisfaction place reliance, primarily as to indications.

The closest approximation to such a satisfactory study was the somewhat abortive cooperative investigation of the resection of fairly small "closed" nodules; but what I would regard as "premature" judgments prevented the carrying of this study to a successful conclusion. Short of entirely satisfactory answers, however, it is clear that the primary indication for resection is the persistent cavity, especially if the sputum remains "positive"; and I believe that it is seldom indicated to wait longer than about six months before making the decision concerning resection. The so-called "open-negative" cavity is a special aspect of this problem, and fortunately is under special study in a number of centers; but until very adequate data are presented as to the uniform "safety" of such lesions, it is my personal belief that they should be resected whenever possible.

And what of "rest therapy", that oldest and most reliable form of treatment in the pre-chemotherapy days? In the state of North Carolina I have on previous occasions, to a more limited audience than this, had the opportunity to state my beliefs in this regard. Yes, physical rest does have some beneficial influence on the course of nearly all forms of tuberculosis. In my opinion this influence is quite small relative to the influence of drugs, and of such a surgical procedure as resection of a persistent cavity. It is perhaps logical to assume that, if rest has any beneficial value it should also be prescribed. But I submit that, if its role is very minor, as I believe—after having myself practiced a very strict form of bed rest for many, many years—its contribution may be very little needed.

And we must not overlook the fact that we paid a price for strict bed rest. True, at that time the results were worth the price, but the price tag was there. By prescribing strict rest we deliberately *un*-conditioned our patients, requiring a long *re*-conditioning process at a later date; and, of necessity, we effected profound changes in the psyche of our patients. I submit that these were not small prices to pay; and that it must be demonstrated today that they are worth while if rest is to continue to be used systematically. I know of no such demonstration, and considerable evidence to the contrary—that little restriction of physical activity is required, and that *only* "a little" may actually be beneficial. By this I do not mean that hospital therapy for the majority of cases of active tuberculosis is not indicated. On the contrary, I think the evidence is quite clear that it is desirable. But the probable value of this, aside from the public health aspects, is establishing certain aspects of the therapy of tuberculosis as a routine, under constant supervision of a hospital staff—the equivalent of which surely is hard to supply on a home-treatment basis.

If it is permissible, or desirable, to treat patients with active tuberculosis with much less restriction of physical activity, and thus with less unconditioning, it is clear that less reconditioning is indicated. The corollary to less rest is the lessened need for what has been called "rehabilitation." Our carefully thought-out and implemented programs of rehabilitation were in large part a reflection of our

uncertainty as to the end point of therapy, and also a reflection of the high relapse rate prior to the advent of effective chemotherapy. If it is safe greatly to shorten the rehabilitation period without harm to the patients, clearly this is desirable from many standpoints. It is incumbent upon us all to keep a very open mind upon this point, without necessarily too much adherence to traditions from the pre-chemotherapy era.

I quoted Dr. Muschenheim as saying that we can't wait for follow-up data to make decisions, which certainly is true. Yet this absolves none of us from the obligation to conduct follow-up studies. In February of this year Dr. Bachrach presented at the Chemotherapy Conference in Memphis the results of a five-year follow-up of cases treated in 1951 with an average of nine to twelve months of streptomycin-PAS therapy. In contrast with results reported on these patients at earlier dates, after one and two years of observation, it was noted that some 20 per cent of all patients had died (not all of tuberculous causes), and that approximately 20 per cent of the survivors still had tuberculous disease judged to be active. Of especial interest was the finding that these late results were clearly related in particular to two variables at the start of treatment: age of the patient and size of the largest cavity, and that of these two the former appeared to have the larger association. When tuberculous and nontuberculous deaths were separated, it was found that there was no excess or deficit of the latter from that rate anticipated; tuberculous deaths, on the other hand, exceeded "expected" deaths (from life tables) particularly in the first three years after the start of treatment. This kind of a follow-up study, although applied to a form of treatment little used today—streptomycin and PAS for an average of less than a year—nevertheless clearly has demonstrated our need to concentrate therapeutic efforts to a greater extent on older age groups and on patients with the larger tuberculous cavities. There will be a continuing need to study our clinical results over long periods that we may still further highlight those areas in the broad spectrum of tuberculosis wherein our results are the least satisfactory and where therapeutic efforts need to be intensified.

* * *

I am grateful to Dr. Muschenheim for having unwittingly three years ago served as the stimulus for these remarks this evening. I am grateful to the North Carolina Trudeau Society for having given me the opportunity to make them.

PASSIVE TRANSFER OF THE DELAYED DERMAL SENSITIVITY TO TUBERCULIN BY MEANS OF BLOOD LEUKOCYTES[1,2]

The Impedient Effect of Specific Desensitization

A. OLIVEIRA-LIMA

(Received for publication March 24, 1958)

Introduction

There is general agreement that the delayed inflammatory reaction of tuberculin hypersensitivity results from interaction of the antigen with sessile antibodies of the sensitized cells.

The first studies on passive transfer of tuberculin hypersensitivity suggested that successful transfer required intact and viable cells. Recent experiments (1, 2, 3) have shown, however, that this transfer may be accomplished by injection of extracts from sensitized cells.

In a limited number of trials, Kirchheimer and associates (4) found that desensitization of tuberculous guinea pigs with tuberculin tends to abolish the capacity of their peritoneal cells to transfer passively the sensitivity to tuberculin. It was suggested that these experiments, if reproducible, would provide evidence that desensitization with tuberculin might result from saturation of fixed cellular antibodies by tuberculoproteins.

It is the purpose of this report to present evidence indicating that specific desensitization of human beings who are hypersensitive to tuberculin will suppress the capacity of their blood leukocytes to transfer passively the delayed skin sensitivity to tuberculin.

Material and Methods

Technique of obtaining leukocytes: The concentrates of viable leukocytes were obtained following the recommendations of Lawrence (5, 6). Approximately 100 ml. of venous blood of each donor were drawn. The leukocytes were not refrigerated or stored and were injected into the recipients within four hours after collection.

Tuberculin: The tuberculin preparation used was standard Old Tuberculin (OT).[3]

Streptococcal antigen: A pure culture of beta hemolytic streptococcus, Type 3, was grown in 100 ml. of beef-infusion broth for twenty-four hours, centrifuged, washed three times with saline, resuspended in saline, and heated at 56°C. for one hour. The suspension was adjusted to contain approximately 150 million cells per ml. One-tenth milliliter of this suspension was used as a skin-test dose.

Selection of donors: The group of donors was composed of 6 male subjects aged twenty-five to forty-two years, all having a normal leukocyte count. These subjects were employed as leukocyte donors both before and after desensitization with tuberculin.

Before starting desensitization, all subjects were re-tested with tuberculin and found to be reactive to 0.1 ml. of 1:1,000 OT intradermally, with 2-plus or 3-plus reaction at

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[1] From the Allergy Section, Department of Internal Medicine, National School of Medicine, Rio de Janeiro, Brazil.

[2] Supported by a grant from the National Research Council of Brazil.

[3] Obtained from Lederle Laboratories Division, American Cyanamid Co., Pearl River, New York.

forty-eight hours. In quantitative intradermal tests with serial dilution of tuberculin, it was found that 4 subjects elicited 2-plus reaction up to 1:10,000 OT, and 2 showed a 1-plus reaction up to 1:100,000 OT.

The tuberculin tests were performed in the flexor surface of the forearm, and the reactions were measured and recorded according to the standards of the National Tuberculosis Association (7).

The criteria recommended by Lawrence (6) were adopted for performing and reading the tests with the streptococcal antigen. Four donors showed 2-plus or 3-plus reactions at forty-eight hours to intradermal injection of 0.1 ml. of a suspension containing 15 million cells per ml.

Selection of recipients: The recipients selected for passive transfer of leukocytes comprised 12 white normal adults ranging from twenty to thirty years in age. They were not reactive at twenty-four, forty-eight, seventy-two, and ninety-six hours to intradermal injection of 0.1 ml. of 1:100 OT. All recipients were skin-tested with tuberculin on two occasions, at fifteen-day intervals.

Ten of these recipients were also nonreactive at twenty-four to forty-eight hours to intradermal injection of 0.1 ml. of streptococcal suspension containing 15 million cells. Recipients *R10* and *R11* showed 2-plus reaction to this antigen at forty-eight hours. The last tests with tuberculin and Streptococcus were done ten to fifteen days prior to leukocytic transfer.

Technique of desensitization with tuberculin: The technique of Brownlee and Madigan (8), with slight modification, was employed for the desensitization with tuberculin. Heat-killed BCG (Moreau strain), defatted according to the procedure of Anderson (9), was used as a substitute for integral heat-killed tubercle bacilli. Defatted bacilli were employed in order to avoid local necrosis or abscess formation, and because the protein antigenicity of the treated bacillary body has been shown to be undamaged by lipid solvents (10, 11).

The desensitization material comprised a suspension of defatted BCG together with OT. The injections were made intramuscularly. The initial dose contained 0.001 mg. of OT and 1×10^{-6} mg. of bacillary bodies per ml. The amount of the suspension was increased by daily increments until the dose of 10.0 mg. of OT and 0.01 mg. of tubercle bacilli were injected. The last dose was repeated until a complete disappearance of any local or systemic reaction occurred. At the end of fifty to ninety days, all 6 patients were found to be desensitized to 10.0 mg. of OT injected intramuscularly. By this time it was possible to inject all patients with 10.0 mg. of OT intradermally without any noticeable local reaction after forty-eight to seventy-two hours.

Technique for testing the tuberculin-neutralizing capacity of serum: The technique of Wells and Wylie (12) was employed, with minor alterations. The sera from the 6 tuberculin-desensitized patients were filtered through a Seitz filter and kept without preservative in the refrigerator for twenty-four to forty-eight hours. Three dilutions of OT (1:100, 1:1,000, and 1:10,000) were prepared in sterile saline solution, and to 0.1 ml. of each dilution 0.9 ml. of the serum to be investigated was added. The same dilution of tuberculin made up with saline and the sera to be tested with saline were employed as controls.

The tuberculin dilutions, both test and control, were allowed to stand at room temperature for forty-eight hours and were tested for sterility before use. Six tuberculin-hypersensitive subjects were selected as recipients. Their degrees of skin reactivity to tuberculin were determined by intradermal tests with serial dilutions of OT. Each recipient was challenged intradermally on the forearm with 0.1 ml. of the three tuberculin dilutions (1:100, 1:1,000, and 1:10,000) made up with serum, and with the control material. The tests were read at forty-eight hours, and the diameter of the indurated areas was measured in millimeters.

Passive Transfer of Tuberculin-Sensitivity to Tuberculin-desensitized Patients

To test the possibility of transferring the delayed tuberculin sensitivity to tuberculin-desensitized recipients, 4 desensitized subjects were employed as recipients of leukocytes from 4 hypersensitive donors. The selected donors were normal adults with repro lucible

TABLE 1

RESULTS OF PASSIVE TRANSFER OF THE DELAYED SENSITIVITY TO BOTH TUBERCULIN AND STREPTOCOCCAL ANTIGEN WITH LEUKOCYTES FROM HYPERSENSITIVE DONORS

Donors with Both Tuberculin and Streptococcal Delayed Skin Sensitivity	Nonsensitive Recipients	Packed Leukocytes Injected on Deltoid Areas of Recipients	Skin Reaction on Recipient's Forearm (48 Hours After Cell Transfer) to:	
			0.1 Ml. of 1:1,000 OT	0.1 Ml. Containing 15 Million Streptococcal Cells
		ml.		
AOB	R1	0.20	+++	++
CDC	R2	0.21	++	++
JAC	R3	0.20	+++	+++
MOL	R4	0.18	++	++
AVM	R5	0.19	+++	+++
CSP	R6	0.20	++	++

TABLE 2

ATTEMPTS TO TRANSFER THE DELAYED CUTANEOUS SENSITIVITY TO BOTH TUBERCULIN AND STREPTOCOCCAL ANTIGEN WITH CELLS FROM DONORS DESENSITIZED WITH TUBERCULIN

Donors After Desensitization with Tuberculin	Nonsensitive Recipients	Packed Leukocytes Injected on Deltoid Areas of Recipients	Skin Reaction on Recipient's Forearm (48 Hours After Cell Transfer) to:	
			0.1 Ml. of 1:100 OT	0.1 Ml. containing 15 Million Streptococcal Cells
		ml.		
AOB	R7	0.20	0	++
CDC	R8	0.21	0	++
JAC	R9	0.19	0	++
MOL	R10*	0.20	0	++
AVM	R11*	0.19	0	+++
CSP	R12	0.20	0	++

* Recipients reactive 2+ to streptococcal antigen before cell transfer.

2-plus to 3-plus forty-eight-hour reactions to 0.1 ml. of 1:1,000 OT injected intradermally.

The cutaneous anergy of recipients was checked with 0.1 ml. of 1:10 OT ten days prior to the injection of sensitized cells. Each recipient was injected subcutaneously in the deltoid area with 0.20 to 0.22 ml. of the donors' leukocytes in 1.0 ml. of Hanks' solution. Forty-four hours later they were challenged intradermally with 0.1 ml. of 1:100 OT on the surface of the forearm. The results are presented in condensed form in table 3.

RESULTS

The results of the experiments summarized in tables 1 and 2 clearly show that leukocytes from tuberculin-hypersensitive subjects lose their capacity to transfer the delayed tuberculin sensitivity soon after their donors become specifically desensitized. These results indicate that the lack of skin response to tuberculin obtained by repeated increasing doses of the desensitizing substance was not the simple result of a nonspecific alteration of the cutaneous vascular

reactivity. It was accompanied by a simultaneous disappearance of cellular hypersensitivity to tuberculin.

That this desensitization induced by treatment with tuberculin is specific in nature can be inferred from the results of experiments presented in table 2. These results show that the delayed skin sensitivity to streptococcal antigen exhibited by the donors prior to desensitization remained unchanged after desensitization with tuberculin, and could regularly be transferred to normal nonsensitive recipients.

In table 3 are summarized the results of experiments delineated to explore the possibility of transferring the delayed sensitivity to tuberculin to tuberculin-desensitized subjects by means of leukocytes. According to these results, the anergic reaction to tuberculin did not exert any effect on passive transfer of sensitivity to tuberculin. In this respect the desensitized subjects behaved like normal recipients.

The results of the experiments to study the tuberculin-neutralizing capacity of sera from tuberculin-desensitized patients are presented in table 4. As can be seen, the attempts to find tuberculin-neutralizing antibodies in the sera of the desensitized subjects were fruitless, even when tuberculin was employed in high dilution.

TABLE 3

ATTEMPTS TO TRANSFER THE DELAYED SENSITIVITY TO TUBERCULIN TO TUBERCULIN-DESENSITIZED RECIPIENTS BY MEANS OF LEUKOCYTES

Donor's Tuberculin Sensitivity to 0.1 Ml. of 1:1,000 OT	Tuberculin-desensitized Recipients	Packed-Leukocytes Injected on Deltoid Areas of Recipients	Skin Reaction on Recipient's Forearm to 0.1 Ml. of 0.100 OT (48 Hours After Cell Transfer)
		ml.	
D1 +++	AOB	0.20	+++
D2 +++	CDC	0.20	++
D3 ++	JAC	0.19	++
D4 +++	MOL	0.22	++

TABLE 4

RESULTS OF EXPERIMENTS TO STUDY THE TUBERCULIN-NEUTRALIZING CAPACITY OF SERA FROM TUBERCULIN-DESENSITIZED PATIENTS

Tuberculin Hypersensitive Recipients	Forty-eight-Hour Skin Reaction (mm.) to Intradermal Injection of 0.1 ml. of:							
	Tuberculin plus test serum			Serum from:	Tuberculin plus saline			Serum plus saline
	Mg. of tuberculin (OT) injected				Mg. of tuberculin injected			
	0.1	0.01	0.0001		0.1	0.01	0.001	
R20	20 × 20	17 × 15	8 × 8	AOB	21 × 21	16 × 15	7 × 7	0
R30	18 × 20	15 × 15	7 × 8	CDC	17 × 18	13 × 14	6 × 7	0
R40	22 × 18	14 × 13	5 × 5	JAC	21 × 18	13 × 13	5 × 5	0
R50	19 × 18	13 × 13	5 × 4	MOL	18 × 18	13 × 13	5 × 6	0
R60	20 × 18	12 × 12	6 × 4	AVM	19 × 19	13 × 12	6 × 5	0
R70	18 × 17	13 × 12	5 × 5	CSP	18 × 19	12 × 12	4 × 5	0

Discussion

In spite of the fact that some aspects of the mechanism of delayed tuberculin hypersensitivity have been clarified in the last years, we are not yet in a position to speak with certainty about the mechanism of the specific desensitization obtained in this condition. It is known that conventional antibodies may appear in the serum of animals exposed to live or dead *M. tuberculosis*, or to its purified antigens. However, none was shown capable of inhibiting the characteristic delayed reaction produced by tuberculoprotein in hypersensitive tissues.

It is believed that some kind of cellular antibody is involved in delayed tuberculin hypersensitivity and that the tuberculin reaction is the result of the interaction of this sessile antibody with tuberculoproteins. It is thus reasonable to assume that the desensitization obtained through tuberculin therapy might be the result of a specific saturation of these sessile antibodies. Unfortunately, this hypothesis is not yet open to a direct approach since there is no method for quantitative evaluation of this kind of antibody.

That the desensitization obtained by repeated doses of tuberculin is specific in nature is indicated by the finding that it is not accompanied by a simultaneous desensitization to other antigens. The delayed skin sensitivity to streptococcal antigen exhibited by the donors remained unchanged after tuberculin desensitization, and could be regularly transferred to normal recipients by means of cells (table 2).

It remains to be determined how the interaction comes about between tuberculin and sessile antibodies. It has been postulated that the antibody in delayed tuberculin hypersensitivity is an intrinsic part of certain cells, to which it remains bound. Recent studies (1, 13) have shown, however, that the "cell factor" involved in the transfer of the delayed type of hypersensitivity may be freed from cells under relatively mild conditions and without evidence of extensive morphologic damage to cells. The correlation that might exist between the "cell factor" responsible for transferring the delayed tuberculin sensitivity and the plasma factor described by Cole and Favour (14) remains a matter for speculation.

The assumption that the cells of a specifically desensitized individual may become temporarily exhausted or blocked in their capacity to produce sessile antibodies is consistent with the finding that tuberculin desensitization is only accomplished after injection of large doses of tuberculin. The present results, showing that the leukocytes of patients desensitized to tuberculin temporarily lose the capacity to transfer their primitive tuberculin sensitivity to normal recipients, appear to be a new argument in favor of this hypothesis.

A similar suppression of immune response with blockade of antibody production can be found in other experimental conditions (15, 16, 17). An "immunologic paralysis" (16) or an "immunologic unresponsiveness" (17) can be induced in experimental animals by injection of large doses of heterologous antigens.

It is generally assumed that, when the antigen taken up by the antibody-producing cells is more resistant to intracellular enzymes, as exemplified by

pneumococcal polysaccharide, it may persist in these cells for a long period of time (18). If the antigen is a protein by nature, one would expect its rapid disappearance by intracellular proteolysis. In that case, repeated and large doses of antigen should be employed to achieve the exhaustion of sessile antibodies. In any case, the specific refractoriness obtained in man after desensitization with large and repeated doses of tuberculin appears to be similar to that obtained in the experimental animal injected with very large doses of protein antigen.

Summary

It was shown that the leukocytes of human beings hypersensitive to tuberculin lose the capacity to transfer passively the delayed dermal sensitivity to tuberculin soon after their donors become specifically desensitized. The desensitized state obtained after repeated intramuscular injections of large doses of Old Tuberculin, together with defatted tubercle bacilli, was shown to be specific in nature, since it was not accompanied by a simultaneous desensitization to a streptococcal antigen. It was not possible to detect the presence of any tuberculin-inhibiting antibody in the sera of the desensitized patients. It was suggested that the desensitization obtained with injections of large doses of tuberculin might be the result of specific exhaustion of sessile antibodies by tuberculoproteins.

Sumario

Transferencia Pasiva de la Dermosensibilidad Retardada a la Tuberculina por Medio de los Leucocitos Sanguíneos

Queda aquí demostrado que los leucocitos sanguíneos de seres humanos hipersensibles a la tuberculina pierden su capacidad para transferir pasivamente la dermosensibilidad retardada a la tuberculina poco después de quedar sus donantes desensibilizados específicamente. El estado desensibilizado obtenido después de repetidas inyecciones intramusculares de grandes dosis de tuberculina antigua, junto con bacilos tuberculosos desgrasados, resultó ser específico en su naturaleza, pues no se acompañó de desensibilización simultánea a un antígeno estreptocócico. No fué posible descubrir la presencia de ningún anticuerpo inhibidor de la tuberculina en el suero de los sujetos desensibilizados. Señálase que la desensibilización obtenida con inyecciones de grandes dosis de tuberculina podría ser la consecuencia del agotamiento específico de los anticuerpos sésiles por tuberculoproteínas.

Resume

Transfert passif de la sensibilité dermique tardive à la tuberculine au moyen de leucocytes sanguins

Il a été démontré que les leucocytes du sang prélevés chez des humains, présentant une hypersensibilité à la tuberculine, perdent la capacité de transférer passivement la sensibilité dermique tardive à la tuberculine dès que les donneurs deviennent spécifiquement désensibilisés. L'état de désensibilisation, obtenu après injections intramusculaires répétées de larges doses de tuberculine de Koch avec adjonction de bacilles tuberculeux dégraissés, a démontré sa non-spécificité du fait qu'il ne s'accompagnait pas d'une désensibilisation concomitante à un antigène streptococcique. Il n'a pas été possible de déceler la présence d'un anticorps quelconque inhibiteur de la tuberculine dans le sérum des patients désensibilisés. L'article suggère que la désensibilisation obtenue avec des injections de hautes doses de tuberculine pourrait être le résultat d'un épuisement spécifique d'anticorps sessiles par les tuberculo-protéines.

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THE PATHOGENESIS OF THE HAMMAN-RICH SYNDROME[1, 2]

A Review from the Standpoint of Possible Allergic Etiology

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Introduction

The syndrome of diffuse interstitial pulmonary fibrosis of unknown etiology was first described by Hamman and Rich in 1935 (1), and since that time increasing numbers of cases have been reported. Several cases of the syndrome are seen each year in larger pulmonary clinics, and the condition can no longer be regarded as a rare one. Increasing recognition of the syndrome has accompanied wider use of detailed study of lung function and diagnostic lung biopsy.

The essential pathologic lesion of diffuse interstitial pulmonary fibrosis consists of fibrotic thickening of the alveolar septa throughout all lobes of both lungs, leading to a condition of alveolocapillary block. The chief clinical features, dyspnea and cyanosis, are dependent upon this, and they are often accompanied by clubbing of the fingers, cough, hemoptysis, and fine crepitations scattered over all areas of both lungs.

Originally regarded as following an acute course resulting in death from respiratory insufficiency or right-sided heart failure within six months, it is now realized that the syndrome may present all degrees of severity and acuteness. Symptoms may remain unaltered for long periods, but recurrent exacerbations of cough, dyspnea, and cyanosis are characteristic, as is transition from a state of prolonged but minimal dyspnea into a phase of steady deterioration.

The "classic" histologic appearance in the lungs, i.e., established alveolar wall fibrosis, is almost the pathologic end stage. It is possible to trace a sequence of histologic changes leading to this established fibrosis. The earliest lesion described consists of exudation of small to moderate amounts of serofibrinous fluid into the alveolar septa and spaces. Some clinicians describe this as containing few or no cells, but others have reported the presence of polymorphonuclear leukocytes in the same sites (2–4). Frank intra-alveolar hemorrhage accompanies the exudate.

In the next stage the mononuclear cell (pulmonary macrophage, pulmonary histiocyte) is the dominant cell. The alveolar walls are thickened by infiltration of such cells within their substance and on their surface, and clusters of similar cells lie free in the alveolar spaces (figure 1*A*). The alveoli may contain only a few macrophages and erythrocytes or there may be abundant fluid and fibrin as well as numerous eosinophils. In the next—or most classic—stage, the alveolar

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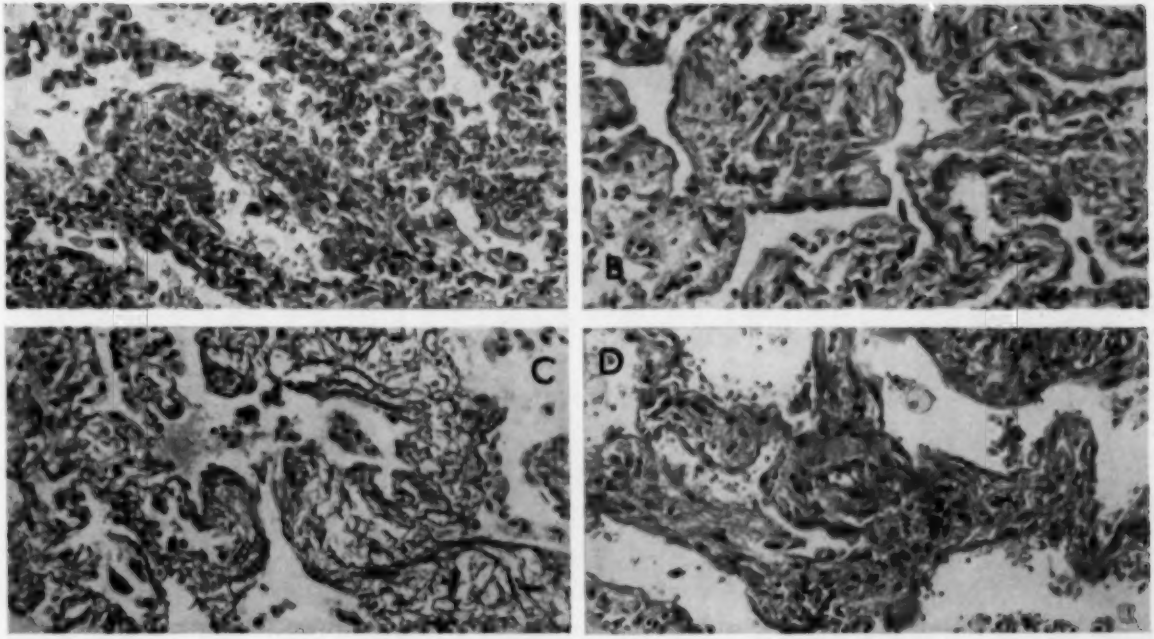

FIG. 1. Sections of lung from cases of the Hamman-Rich syndrome. (*A*) Early phase: alveolar walls thickened by mononuclear cell infiltration.(*B*) "Classic" appearance: septa thickened by cellular connective tissue; partial alveolar epithelial linings. (*C*) Same stage as previous section stained with Laidlaw's stain to show reticulin hyperplasia. (*D*) Advanced lesions: collagenous alveolar septa. (All sections, ×400).

septa are thickened by cellular connective tissue. Mononuclear cells and fibroblasts are present in various proportions, and alveolar spaces are lined by a continuous layer of prominent cuboidal epithelium. Alveolar wall capillaries are described by most writers as dilated, as collapsed and bloodless by others (5, 6).

Increased deposition of connective tissue leads to gross alveolar wall thickening (figure 1*B*). The thickening, while diffuse, is not uniform, and localized nodules in the walls are not uncommon. The increase of connective tissue is accompanied by a decrease in cellularity of the septa and reduction in size of alveolar spaces, which contain fewer cells than previously. Silver staining reveals (figure 1*C*) that the bulk of the new connective tissue is reticulin in type. Golden and Bronk (7) noted this appearance as well as a striking increase in the number and size of alveolar wall capillaries and referred to it as "a condition of reticulosis and angiosis of the alveolar septa." Giant cells of the Langhans' type are a frequent but not constant feature.

Some regard these as the final histologic appearances of the Hamman-Rich syndrome. Should the patient survive for a sufficient time, however, collagen is deposited in the alveolar walls (figure 1*D*), which become more dense, less cellular, and somewhat thinner. Hyperplastic alveolar epithelium and alveolar wall capillaries are now absent.

At autopsy, and even in lung biopsy specimens, the changes are seldom uniform throughout all areas. Rather than claim one or the other stage as characteristic (7), it would seem more profitable to consider the changes in any individual case in terms of the duration and severity of the clinical history.

Review of the Literature

The etiology of the Hamman-Rich syndrome, if indeed there be a single etiology, is obscure, but a number of possible causes have been suggested. Chemical irritation, a possibility advanced by Hamman and Rich (8), has not been supported by any subsequent evidence. Again, three of Hamman and Rich's four patients suffered from syphilis, but the serologic tests for syphilis which have been recorded in almost every subsequent case report have been uniformly negative. A familial occurrence of the condition has been recorded on three occasions—once in twin sisters (9) and in two sets of brothers (10, 11).

Auerbach and associates (12) suggested that chemotherapy interfered with complete resolution of pneumonic exudates and led to a higher incidence of fibroblastic organization. Even allowing the validity of their observations, such organization is predominantly intra-alveolar rather than inter-alveolar in type. Pokorny and Hellwig (13) postulated a failure of fibrinolysin formation based on an unspecified enzyme defect to account for delayed absorption of pneumonic exudate and its subsequent organization. They adduced no evidence to suggest that this was a likely cause for the Hamman-Rich syndrome. Major objections to both of these concepts are the usual absence of an acute respiratory illness, with failure of complete recovery, and the diffuse distribution of the lesions.

Viral infection remains one of the chief etiologic factors suggested. It was first advanced by Hamman and Rich who based the suggestion on their negative or inconstant bacteriologic findings and the novel nature of the pathologic changes. The case reported

by Kneeland and Smetana (5) occurred during a local epidemic of apparent viral pneumonia. Brock (14) based his opinion that the disease was of viral origin on the resemblance of the histologic changes to those of experimental influenzal pneumonia in rabbits and of jaagziekte in sheep. (The only major point of resemblance is the presence of alveolar lining cell hyperplasia.) Later writers (15) have continued to press the possibility of a viral infection; but no evidence, cultural or serologic, has been produced in support of the hypothesis.

Heppleston (4) has advanced good reasons against viral infection as the cause of the syndrome. He has pointed out that in the known viral pneumonias the acute interstitial inflammation and subsequent changes are based on a suppurative bronchiolitis. As a result, the lesions are essentially focal and related anatomically to bronchioles, unlike the diffuse lesions of the Hamman-Rich syndrome. Two comprehensive descriptions of the pathology of primary atypical pneumonia (16, 17) make no reference to interstitial fibrosis of any degree, and the same comment applies to measles and non-measles "giant cell pneumonia" (18).

Peabody and co-workers (9, 19) were the first to suggest the possibility of an "allergic" etiology for the condition, based on the presence of eosinophils in the interstitial tissues. In another paper (10), they cited the similarity of the alveolar wall fibrosis to the pulmonary lesions of scleroderma in support of tissue hypersensitivity. Golden and Bronk (7), on the other hand, distinguished sharply between the collagenous alveolar walls of scleroderma and the "reticulo-angiosis" seen in the Hamman-Rich syndrome. Hinshaw and Garland (20), writing recently on this point, stated: "Since the fibrosis produced has some resemblance to that noted in scleroderma and dermatomyositis, it has been suggested that this may be a localized form of collagen disease. The condition is not associated with other manifestations of collagen disease, which speaks against this being the cause." Grant and associates (21) advanced the occurrence of diffuse interstitial pulmonary fibrosis in hypertensive patients treated with hydralazine (which may also lead to a lupus-like syndrome) as evidence in favor of a hypersensitivity basis for the Hamman-Rich syndrome. Since this change may follow the use of other hypotensive agents (22), it is likely that it is merely due to organization of chronic pulmonary edema fluid in patients surviving longer under treatment. Rubin (23) hinted at a relationship between the Hamman-Rich syndrome and the collagen disease group in discussing four patients with rheumatoid arthritis and diffuse interstitial fibrosis of the lungs; and Rubin and Lubliner (23*a*) have recently amplified this relationship, as well as presenting an excellent review of the whole problem of the Hamman-Rich syndrome.

It is proposed to review briefly those features which suggest that the Hamman-Rich syndrome may be based on immune mechanisms and to supplement this with a comparison between the pulmonary changes in this condition and those occurring in experimental pneumonotoxic pneumonia (24). It is emphasized that the evidence is largely circumstantial and largely based on morphology, but it is nonetheless considerable.

Three of Hamman and Rich's first four patients suffered from syphilis and all three had been treated with arsenical compounds. It has been shown (25) that arsphenamine and neoarsphenamine readily produce anaphylactic phenomena in experimental animals. Two of the patients developed the first symptoms of their fatal illness during, or within several days of completing, a course of arsenical injections, and in these patients fairly recent pulmonary lesions were found at autopsy. The third had been treated with parenteral arsenic fourteen years previously, and in this case the pulmonary changes were those of old, hyalinized fibrosis.

Kneeland and Smetana (5) reported finding the lesions of polyarteritis nodosa in the

pulmonary vessels in their otherwise typical case. This has been dismissed by subsequent writers as an incidental result of the administration of sulfonamides to the patient during the illness. The original protocol, however, reveals that marked urticaria accompanied the onset of respiratory symptoms ten days before sulfapyridine was first administered. It thus seems at least as likely that the allergic vascular lesions were associated with the allergic skin lesions and with the respiratory illness in a common etiology as that they were due to sulfonamide therapy. Katz and Auerbach's (26) patient developed *pari passu* with his respiratory symptoms a migratory and then persistent polyarthritis. The clinical features and skiagrams suggest that this was of the rheumatoid variety. This association will be taken up again later.

The presence of eosinophils in the pulmonary lesions is, at least, compatible with, though not pathognomonic of, allergic inflammation. The same might be said for the hyperglobulinemia which has been present in four (6, 8, 27, 28) of the eight reported cases in which serum protein components have been analyzed. In the absence of disease of other organs, chronic infection and chronic hypersensitivity states remain the chief causes of an elevated serum globulin fraction. The diffuseness of the lung changes suggests that a blood-borne agent is responsible and is again compatible with an immune mechanism or with some as yet unrecognized infective agent.

The familial occurrence of the syndrome, especially when the persons involved have been separated for very many years (9), points to a genetically influenced mode of tissue reaction rather than to a specific infective cause. A familial incidence has been noted in other diseases of presumed "allergic" origin such as rheumatic fever (29). When a familial incidence depends on intimate contact and microbial infection, nonfamilial contact cases are common; but no examples of this phenomenon have been reported in the Hamman-Rich syndrome.

The response of at least some patients to corticotropin or adrenal steroids might be advanced in collateral support of a hypersensitivity hypothesis. There is a general relationship in reported and personally seen cases between the duration of symptoms and response to these agents which is in keeping with the histologic appearances in the lungs. Response is far from universal, but, if it occurs, it persists as long as the drugs are continued in adequate dosage, with severe and often fatal relapse on cessation of therapy (10, 30, 31). This is a pattern well known among diseases of hypersensitivity. No claim can be made that the efficacy of steroid therapy is restricted to examples of allergic inflammation, but the absence of relapse following initial improvement if steroids are continued is unlike the usual behavior of infective processes.

The final feature supporting an immune basis, and one which correlates closely with experimental studies to be discussed, is the morphologic resemblance between various stages of the Hamman-Rich syndrome and lesions which may be found in the lungs in a number of conditions commonly regarded as being based on hypersensitivity. Other writers have drawn attention to the interstitial pulmonary fibrosis occurring in scleroderma (10) and rheumatoid arthritis (23), but it has been objected (7) that this fibrosis is of a different type from that of the Hamman-Rich syndrome. It is hoped to demonstrate that any differences are

largely based on the different age of the process in different diseases. No attempt can be made within the limits of this discussion to justify the inclusion of the various diseases which follow in the "immune basis" group. Acknowledging the widely divergent views held on the etiology of some, all are regarded by a number of competent observers as a manifestation of tissue hypersensitivity.

Polyarteritis nodosa: The pulmonary vessels in polyarteritis nodosa may be involved in up to one-third of the cases (32). While the bulk of pulmonary parenchymal changes are based on infarction or infection, more specific changes have been noted by several observers (33, 34). These have included gross thickening of the basement membrane of alveolar walls with focal fibrinoid necrosis, infiltration of the alveolar septa by mononuclears and giant cells, and fibroblastic proliferation in the intralobular septa.

Systemic lupus erythematosus: Many of the pulmonary changes in lupus erythematosus are infective in origin, but Tumulty and Harvey (35) and Harvey and associates (36) have described a more specific "lupus pneumonitis." Sections from several of the former group of cases were described by Rich as showing an "anaphylactoid type of pneumonitis," a term which he uses to embrace that form of pneumonia seen in serum sickness and in acute rheumatism (*see* below). Similar changes have been reported by Rakov and Taylor (37) and Foldes (38), while organization of the interstitial pneumonia was observed by Harvey and associates (36).

Wegener's (or pathergic) granulomatosis: The specific features of Wegener's granulomatosis are a focal vasculitis and granulomatous lesions in which greater or lesser amounts of necrosis have occurred. Giant cells and eosinophils are constant components of these lesions. Equally well documented are interstitial lesions in the lungs. The alveolar walls are widened by infiltrations of large mononuclears, plasma cells, and eosinophils, and the alveolar spaces are lined by cuboidal epithelium. These changes are followed by proliferation of fibroblasts and reticulin fibrils (well illustrated by Walton and Leggatt (39)), and eventual alveolar wall fibrosis (40). Churg and Strauss (41) and Ehrlich and Romanoff (42) have noted granulomatous nodules protruding from alveolar septa and covered by a continuous layer of alveolar lining cells. Fienberg (40) has defined an "idiopneumonic" group of cases of this condition in which pathologic changes are confined to the lungs for long periods or even permanently.

Rheumatic disease: Rheumatic involvement of the lung is far from universally accepted as an entity, although many careful studies in the past twenty-five years have established a constant pattern of pathologic changes (43, 44). The acute stages are marked by focal fibrinoid necrosis of alveolar septa, hyaline capillary thrombosis, focal intra-alveolar hemorrhage, and exudation of fluid and fibrin containing scanty polymorphonuclears and more frequent mononuclears. The destructive stage is immediately succeeded by a stage of proliferation of large mononuclear cells, some of them multinucleated. These cells balloon out the alveolar walls, and lie free in alveoli as pulmonary macrophages. So-called Masson bodies (45) are characteristic but not specific (46). They protrude as buds from the alveolar septa, are composed of varying proportions of fibrin and cells, and are often covered by a layer of cuboidal epithelium.

The subacute stages are marked by proliferation of fibroblasts within the alveolar septa, and this process has been demonstrated as early as three weeks after the onset of an initial attack of acute rheumatic fever (47) before any question of chronic venous congestion of the lungs arises. The persistence of hyperplastic alveolar epithelium on these cellular alveolar walls sometimes leads to a pseudo-glandular appearance, but with increasing deposition of interstitial fibrous tissue both alveolar epithelium and alveolar wall capillaries diminish markedly. Large or small foci of intra-alveolar organization are seen, but the final picture is essentially one of extensive collagenous fibrosis of the alveolar septa (43). As long ago as 1947 Muirhead and Haley (48) commented on the similarity of the histologic appearances in one of their cases to those described by Hamman and Rich.

Acute glomerulonephritis: Reports of pulmonary involvement in glomerulonephritis apart from terminal pulmonary edema and infection, are uncommon. The best account is that of Parkin and associates (49) who reported 7 cases studied at autopsy. In the most acute stages there was an "acute necrotizing alveolitis" with focal fibrinoid necrosis, hemorrhage, and exudation of polymorphonuclears. There followed a "focal thickening of the alveolar wall by loose connective tissue in which scattered lymphocytes and macrophages" were present. In the final stage the alveolar walls were thickened by heavy collagenous bundles. Other sporadic reports of similar changes have appeared (12, 50).

Rheumatoid arthritis: Ellman and Ball (51), Rubin (23), and Read (52) have reported a total of 7 cases of classic rheumatoid arthritis; all of the patients had diffuse interstitial pulmonary fibrosis quite indistinguishable histologically from that reported by Hamman and Rich. The patient with the "Hamman-Rich syndrome" reported by Katz and Auerbach (26) was almost certainly suffering from rheumatoid arthritis. Christie (53) has drawn attention to rather more acute and focal lesions, including rheumatoid nodules and Masson bodies, in the lungs of three patients with rheumatoid arthritis.

Scleroderma: Kraus (54) and Getzowa (55) have reported a very cellular interstitial pneumonia in scleroderma with a glandlike overgrowth of the alveolar epithelium, preceding true fibrosis of the alveolar septa. The septa eventually lose all cells and vessels, become hyalinized, attentuated, and finally rupture to give rise to the classic cystic sclerosis. Evidence of an allergic basis for scleroderma, of course, rests on far less sure ground than for the other conditions referred to above.

Discussion

There is thus considerable morphologic resemblance between the pulmonary lesions in all of the diseases discussed and those of the Hamman-Rich syndrome if account is taken of the age and intensity of the process. Both groups show in the earliest phases an acute reaction involving primarily the alveolar septa, with some "overflow" into alveolar spaces. Alveolar wall necrosis, a feature of some of the disease states, is absent in the Hamman-Rich syndrome. Mononuclear cell proliferation (with occasional giant cell formation) in both spaces and septa follows, with prominence of the alveolar lining epithelium. Fibroblasts invade

the alveolar walls, and reticulin and (finally) collagen are deposited in increasing amounts. Interstitial fibrosis, with hyalinization and loss of capillaries and cellular elements, occurs in the chronic stages.

The tempo of the pathologic process, its duration, and the life-span of the patient determine which phases of the process will be seen in both groups. Thus the age of the changes in the Hamman-Rich syndrome accords moderately well with the clinical history. In those examples of "allergic" disease which run an acute course in their fatal forms (polyarteritis nodosa, lupus erythematosus, and acute nephritis) only acute changes may be seen. Subacute lesions are usually well marked in Wegener's granulomatosis. The changes in chronic diseases such as rheumatoid arthritis are indistinguishable from the classic lesions of the Hamman-Rich syndrome, and in scleroderma even more advanced lesions may be noted. A disease such as rheumatic fever which may prove fatal at many different stages of development illustrates all phases of the process.

This circumstantial evidence is lent further support by the occurrence of a similar pathologic process in recent experimental studies of tissue allergy in the lung (24). Pneumonotoxic pneumonia (analogous with nephrotoxic nephritis) has been produced by intratracheal injection of rabbit anti-rat-lung serum in rats, and acute, subacute, and chronic changes were studied from a few hours up to six weeks later.

In the earliest stages there was exudation of fluid and fibrin; and neutrophils, eosinophils, and mononuclears clustered about the alveolar septa (figure 2*A*). Neutrophils rapidly disappeared, leaving an exudate composed of large mononuclear cells with vesicular nuclei, among which eosinophils remained prominent for thirty-six to forty-eight hours (figure 2*B*). The alveolar septa were thickened at first by capillary dilatation, interstitial edema, and cellular infiltration, but by the end of forty-eight hours the first two factors had subsided and large mononuclear cells alone ballooned out the septa. In the earliest stages the reticulin framework of the lung was intact, but by seventy-two hours focal fragmentation of alveolar wall reticulin were occasionally seen.

On the third day after injection a clear distinction could be made between intra-alveolar histiocytes and the greatly thickened alveolar walls (figure 2*C*). The walls contained many ovoid mononuclears, and alveolar spaces were lined by a well-defined epithelial layer. The lung had taken on a glandular appearance. Buds were seen protruding from the walls of alveoli and alveolar ducts as early as twenty-four hours after the injection of serum, and they increased in size and number over the next few days. Some (figure 2*D*) were predominantly cellular, had a well-marked stalk of attachment, and were covered by a layer of cuboidal cells. Others (figure 2*E*) were more fibrinous and less well defined.

After four days, increasing numbers of fibroblasts appeared in the thickened septa (figure 3*A*) and capillaries and alveolar epithelium were far less prominent. Langhans' giant cells (figure 3*B*) were present in large numbers. Occasional areas of necrosis were seen on the fourth day (figure 3*C*). In these might be discerned the "ghosts" of cell bodies and alveolar septa, as well as considerable nuclear debris. Fibroblasts and ovoid mononuclears sometimes showed palisading at the borders of the lesion. No unequivocal examples of arteritis were produced.

Progression was primarily interstitial. Increasing numbers of fibroblasts appeared in the alveolar septa, which were thickened by these cells and by increasing amounts of connective tissue (figure 3*D*). Silver staining showed this connective tissue to be largely reticulin in type (figure 3*E*). The final picture was one of dense fibrosis of alveolar walls which were often

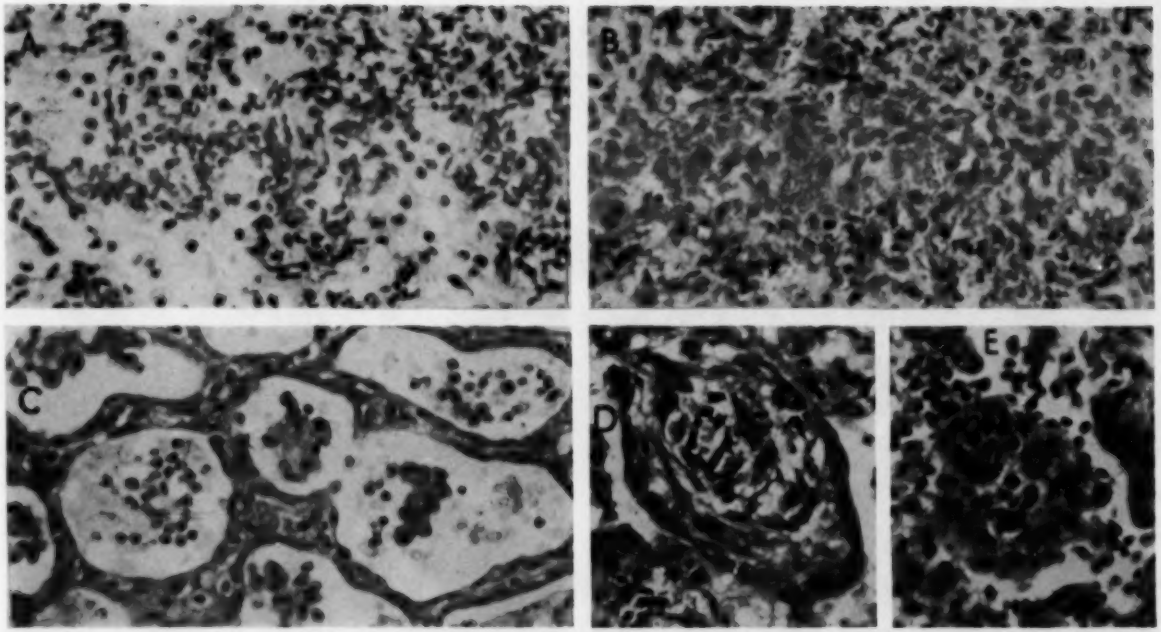

FIG. 2. Sections of rat lung illustrating experimental pneumonotoxic pneumonia, following intratracheal injection of rabbit anti-rat-lung serum. (*A*) Eight hours after injection, polymorphonuclears clustered about the septa. (*B*) Forty-eight hours after injection whole lung substance infiltrated with mononuclears. (*C*) Seventy-two hours after injection, septa was thickened by monuclear cell infiltration. (*D*) Cellular and (*E*) fibrinous budlike lesions. (All sections, ×400).

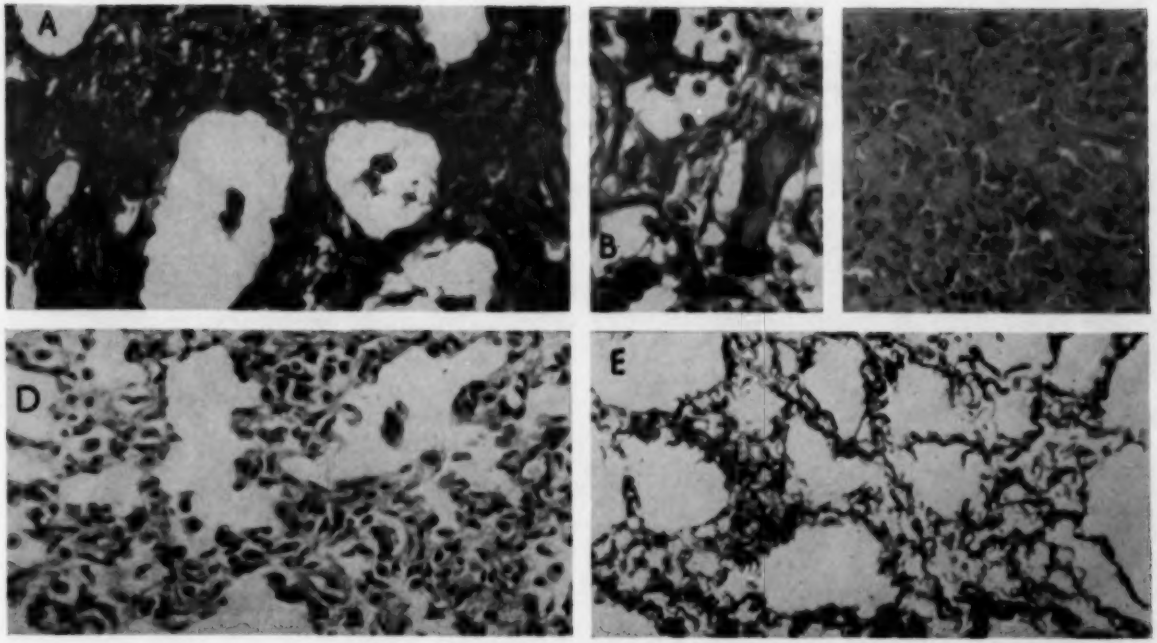

FIG. 3. Sections of rat lung illustrating progression of pneumonotoxic pneumonia. (*A*) Four days after injection, fibroblasts invaded the alveolar septa. (*B*) Langhans' giant cells. (*C*) Tissue necrosis with palisading at borders. (*D*) Two weeks after injection, interstitial pulmonary fibrosis. (*E*) Three weeks after injection, gross reticulin hyperplasia in septa.

thinner, less cellular, and more condensed than previously. Large amounts of collagen might be demonstrated by appropriate staining, while alveolar epithelium and alveolar wall capillaries disappeared.

An Arthus type of reaction has been previously described in the lungs (56), but pneumonotoxic pneumonia has many features of difference from a simple Arthus reaction and from the lesions described by Rich (57) following large intravenous injections of foreign protein. It is postulated that this immune type of pneumonitis provides an experimental link between the Hamman-Rich syndrome, on the one hand, and diseases of probable immune origin, on the other.

Without repetition it will be apparent that many of its features are those described in human disease in the preceding pages. Obvious focal fibrinoid necrosis is absent, but focal fragmentation of alveolar wall reticulin may well be its counterpart. The lesions illustrated in figures 2*D* and 2*E* are presented as the experimental equivalent of the Masson body and of the bulbous septal granulomas of Wegener's granulomatosis. They probably bear some relation to the allergic granuloma of Goddard (58), for they appear much too quickly to represent organization phenomena. The necrotic lesion in figure 3*C* may be the prototype of the necrotic granuloma of Wegener's granulomatosis or even of the rheumatoid nodule. The Langhans' giant cells (figure 3*B*) correspond to those of Wegener's granulomatosis and the Hamman-Rich syndrome. Comparison of sections from cases of the Hamman-Rich syndrome with those of pneumonotoxic pneumonia shows considerable morphologic resemblance at all stages at which they may reasonably be compared. Features of correspondence are summarized in table 1.

TABLE 1

COMPARISON OF FEATURES OF HUMAN "ALLERGIC" PULMONARY DISEASE WITH THOSE OF PNEUMONOTOXIC PNEUMONIA

Human Disease	Features in Common with Pneumonotoxic Pneumonia
Polyarteritis nodosa, lupus erythematosus, acute nephritis	Destructive alveolar wall lesions; exudate of fibrin and polymorphonuclears; focal hemorrhage; mononuclear cell permeation of alveolar walls and spaces
Wegener's granulomatosis	Necrotic granulomas; granulomatous alveolar wall lesions; mononuclear and eosinophilic cell exudate; Langhans' giant cells; mononuclear, fibroblast, and reticulin permeation of alveolar septa
Rheumatic pneumonitis	Destructive alveolar wall changes; "Masson bodies"; evolution of alveolar wall changes
Rheumatoid disease	Interstitial pulmonary fibrosis; ? "rheumatoid nodules"
Scleroderma	Interstitial pulmonary fibrosis, finally collagenous
Hamman-Rich syndrome	All stages except for occasional necrotic phenomena

If the premise that at least some examples of the Hamman-Rich syndrome may be based on immune mechanisms is allowed, several possible lines of development of the syndrome might be postulated. It might result from sensitization to external allergens, and the three patients (8) whose symptoms followed treatment with arsenical compounds possibly fall in this group. Isolated manifestations of some of the "collagen diseases" are not unknown in clinical medicine, and again some examples of the syndrome might be manifestations of this phenomenon. The changes of Wegener's granulomatosis are sometimes localized to the lungs (40), and healing examples of this condition would be indistinguishable from the Hamman-Rich syndrome. Of interest in this regard is a case seen by the present writer (reported by Harvey and McGovern (59)) in which diffuse interstitial pulmonary fibrosis was accompanied by rare and scattered renal changes compatible with healed lesions of Wegener's granulomatosis. The condition might represent a post-streptococcal allergic inflammation in its own right (analogous with nephritis or rheumatic disease) or it might be a chronic residuum of the pulmonary changes accompanying one of these two diseases. In this context a young man (a patient of Dr. W. C. B. Harvey) was seen with nonprogressive dyspnea and gross finger clubbing, associated with diffuse bilateral reticular shadows on the chest roentgenogram, all appearing shortly after two attacks of acute rheumatic fever and one of chorea ten years earlier. No lung biopsy was performed; but he had no detectable rheumatic heart disease or other cause for the changes.

Finally it is possible to compromise with those postulating an unusual and unrecognized type of viral infection of the lungs as the cause, and to suggest, as has been done for viral hepatitis (60, 61), that the virus renders the pulmonary parenchymal cells (alveolar lining cells) antigenic, and so leads to changes which are primarily of immune origin.

The various modes of progression of the disease (rapid downhill course; slow progression; arrest for long periods; recurrent exacerbations, some of which lead to temporary or permanent decompensation) are those classically seen in nephritis and rheumatic heart disease, and, if an immune basis is accepted for the three conditions, are doubtless based on similar mechanisms.

Summary

On the basis of experimental studies it is suggested that the phenomena of tissue allergy in the lung follow a fairly constant pattern of evolution to a final stage of interstitial pulmonary fibrosis. Some or all stages of the process may be seen in a number of human diseases currently believed to be based on immune mechanisms, as well as in the syndrome described by Hamman and Rich. It is suggested that the morphologic resemblance of the pulmonary changes in these two groups to each other and to the experimental lesions of pneumonotoxic pneumonia provides additional evidence in favor of the concept that some cases of the Hamman-Rich syndrome are based on immune mechanisms. Features of individual cases of this syndrome have been cited in support of this hypothesis.

Sumario

La Patogenia del Síndrome de Hamman-Rich

A base de estudios experimentales, se apunta que los fenómenos de alergia de los tejidos en el pulmón se conforman a un patrón bastante constante de evolución hasta un período final de fibrosis pulmonar intersticial. Cabe observar algunos de los períodos del proceso, o todos ellos, en varias dolencias humanas consideradas actualmente como basadas en mecanismos de inmunidad, e igualmente en el síndrome descrito por Hamman y Rich. Señálase que la semejanza morfológica de las alteraciones pulmonares en estos dos grupos ya entre sí y también con las lesiones experimentales de la neumonía neumotóxica aporta nuevas pruebas en pro del concepto de que algunos casos del síndrome de Hamman-Rich se basan en mecanismos de inmunidad. En apoyo de esta hipótesis, se citan características de distintos casos de este síndrome.

Resume

La pathogénèse du syndrome de Hamman-Rich

Les études expérimentales permettent de supposer que les phénomènes allergiques se manifestant dans les tissus du poumon ont une évolution d'un type relativement constant jusqu'au stade terminal de la sclérose pulmonaire. Certains des stades, ou tous les stades du processus, peuvent être observés dans quelques maladies humaines couramment considérées comme étant engendrées par les mécanismes de l'immunité, ainsi que dans le syndrome décrit par Hamman et Rich. L'auteur suppose que la ressemblance des modifications pulmonaires dans ces deux groupes entre eux et des lésions expérimentales dans la pneumonie pneumo-toxique sont des signes qui corroborrent l'hypothèse du rôle joué par le mécanisme d'immunité dans certains cas de syndrome de Hamman-Rich. Les aspects de certains cas de ce syndrome corroborrant cette hypothèse sont décrits.

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DETERMINATION OF BILATERAL RESIDUAL VOLUME[1]

1. Examination of Healthy Subjects

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INTRODUCTION

During the past decade it has proved necessary, particularly because of modern thoracic surgery with increasing resection of affected lung tissue, to attempt to get as general a picture as possible of the preoperative pulmonary function. This has entailed a wider use of different methods of examination, chiefly of spirometry and bronchospirometry. With the latter, it is possible to study the distribution of the lung function between the two lungs with respect to the vital capacity (VC), ventilation, and oxygen uptake. With respect to pulmonary function, however, it is of equal, or even greater, value to know the distribution of the functional residual capacity (FRC), residual volume (RV), and total lung capacity (TLC).

For the determination of these lung volumes, there are two methods, viz., the nitrogen-elimination method and the hydrogen- or helium-dilution method.

From a review of the literature, it has been possible to find only two investigations with bronchospirometric determination of these lung volumes (FRC, RV, and TLC) in healthy subjects. In 1952, Gaensler and Cugell (1) published the result of such investigations of four healthy subjects. Since the commencement of the present studies, Svanberg (2), in 1957, made a report on 20 healthy subjects (9 men and 11 women) who could be assessed statistically, his examinations being carried out in different body positions. In both of these investigations the nitrogen-elimination method was used. As far as the present investigators know, the helium-dilution method has hitherto not been used for such studies.

The aim of the present investigation with the helium method in connection with bronchospirometry has been to get from healthy subjects normal figures for the distribution between the lungs of functional residual capacity, residual volume, and total lung capacity, as well as the ratios FRC/TLC and RV/TLC.

METHODS AND MATERIALS

Eight men (23 to 33 years, mean age 27 years) and 8 women (18 to 36 years, mean age 24 years) have been examined. None of the subjects had suffered previously from any lung disease, except for one case of pneumonia without complications. During the last months all of the subjects except 2 were examined with chest roentgenography. The findings were normal, and none of the subjects showed any other clinical signs of disease in the respiratory passages or lungs.

The bronchospirometer used was a double spirograph of Knipping type (Almara®), modified to a volume excl. the bellows of 4.00 liters.

Functional residual capacity was determined with the helium-dilution method as described by Holmgren (3) with a few modifications. As the scale of the catharometer extends

[1] From the Lung Physiology Department, Kolmarden Sanatorium, Sweden.

only to 15 per cent, the initial concentration of helium was about 13 per cent. Furthermore, with the method used by Briscoe (4), oxygen corresponding to 0.25 of the helium volume was added to the helium-air mixture. Finally, a smaller carbon dioxide filter, according to Bates and Christie (5), was placed before the catharometer.

The apparatus was so arranged that the gas mixture was at room temperature when it reached the catharometer.

Spirometry: Spirometry, including the determination of the functional residual capacity with the helium method, was performed in the usual way on all subjects, as far as possible under basal conditions. The subjects, who were fasting, were made to rest for twenty minutes on a couch before the examination, which was performed in the supine position.

Bronchospirometry: Bronchospirometry was carried out in the following way: As premedication the patients were given an injection of 10 cg. of Phenemal® and 1 mg. of atropine three quarters of an hour before the examination was begun. The anesthesia was given in drops in all cases, 4 ml. of 1 per cent Novesin®[2] being used for the pharynx and larynx and 4 ml. of 1 per cent Novesin for the trachea. Carlens' tube was then introduced, No. 37 being used for the women and No. 39 or No. 41 for the men. The examination was performed with the patient in the supine position and was begun at the earliest about five minutes after the intubation. Basal conditions were sought.

Procedure

The examination began with the determination of functional residual capacity, one lung being connected to the spirograph clock containing helium-air mixture and the other lung to the other clock containing oxygen. The reason for taking a spirogram of the other lung at the same time was so that the resting expiratory level would not be changed from the time when one lung was connected to the helium-air mixture and the other lung to the oxygen spirograph.

When the helium concentration had remained constant for about two minutes in the examination of the first lung, the "helium lung" was immediately connected with the oxygen spirograph. About three minutes were allowed to pass before the oxygen lung was connected with the helium spirograph.

After the determination of functional residual capacity, the helium spirograph was rinsed several times with oxygen and then filled with oxygen. Both lungs were then connected with the system, and the ventilation and oxygen uptake were measured for both lungs simultaneously for a four-minute period. All volumes have been given at ambient pressure and saturated with water vapor. Functional residual capacity has been corrected for the volume of the mouthpiece and for possible errors relative to resting expiratory level (always less than 0.10 l.). No adjustment, on the other hand, has been made for the effect of oxygen on the air-helium mixture or for the absorption of helium in blood and tissue.

Discussion

The determination of functional residual capacity has been carried out for one lung at a time. It would probably be possible to make a simultaneous determination for both lungs with only one catharometer by alternately letting the gas mixture of the one feed-circuit pass through the catharometer. With branch tubes and two-way taps placed just at the catharometer the errors connected with this arrangement would probably be negligible. In the present investigation, however, the time value in the dilution was of interest, so that it was necessary to measure functional residual capacity for one lung at a time.

The aim of adding oxygen to the air-helium mixture was to try to get a more stable resting expiratory level by reducing the difference in oxygen-pressure

[2] Beta-dietylaminoetyl-3-butoxy-4-aminobensoathydrochloride.

between the two spirograph gas mixtures. The catharometer is calibrated for helium in air, which in principle implies the introduction of an error in method. However, the magnitude of the admixture has been so adjusted that the error is negligible, as it does not amount to the degree of accuracy with which the instrument can be read, according to what can be calculated from thermal conduction data and has been shown experimentally by Holmgren (3).

The different phases in bilateral FRC-determination according to the method used by the present writers are:

1. Lung I breathes room air and lung II, oxygen.
2. Lung I breathes helium-air mixture and lung II, oxygen, until the helium concentration has remained constant for about two minutes.
3. Lung I breathes oxygen and lung II, room air, for about three minutes.
4. Lung I breathes oxygen and lung II, helium-air mixture, until the helium concentration has remained constant for about two minutes.

During phases 2 and 3, to ensure correct measurement of the distribution of functional residual capacity between the lungs, it is necessary to see that the resting expiratory level does not change. As the supply of oxygen to the helium-air mixture is continuous, to compensate for oxygen consumption, it is not possible definitely to determine changes in the resting expiratory level from the helium-air curve. During phase 2, however, a change can be read off directly in the oxygen spirogram for lung II and correction made for this. During phase 3 the resting expiratory level for lung I is followed on the oxygen spirogram. On the assumption that this does not change without the same also occurring for lung II, it is thereby possible to check the resting expiratory level in this phase for lung II. In case of a change, however, it is not possible to make any correction because, even if the resting expiratory level of the lungs changes with both, the variation is not necessarily of the same magnitude. Summarizing, it may be said that a change in the resting expiratory level in phase 2 can be compensated with correction, while a fluctuation in phase 3 makes it necessary to discontinue the experiment. This has not proved necessary, however, in any case.

The question of the error due to the method in the functional residual capacity determination with the helium method in connection with spirometry on account of the helium absorption has latterly been treated by Holmgren (3) and Birath and Swenson (6). Holmgren (3) has discussed the magnitude of the errors but refrains from making correction for it. Birath and Swenson (6) have arrived at a correction of − 105 ml. for seven minutes' respiration of the helium-air mixture. With the healthy subjects in the present study, the mean value of total lung capacity right was 2.95 l; of functional residual capacity right, 1.20 l; and of residual volume right, 0.75 l. The quotient FRC/TLC is then 1. 20/2.95 = 40.7 and RV/TLC 0.71/2.95 = 24.0. With deduction for 105 ml., the corrected values for FRC/TLC were 1.31/3.06 = 42.8 and for RV/TLC 0.78/3.06 = 26.8. However, the necessary correction is probably less than these 105 ml., which correction holds good for functional residual capacity determination in connection with spirometry, since with successive bilateral FRC determination the

helium concentration in the oxygen lung is near 0. In consideration of this fact, no correction was made for the helium absorption in the tissues.

Besides the ratios FRC/TLC and RV/TLC, the distribution between the lungs of TLC, FRC, and RV has been studied. Here, the helium absorption has very little effect, as blood and tissues have been given about three minutes to get rid of the absorbed amount of helium. During the first minutes the ventilation occurs most rapidly, and the starting point for the two lungs is therefore probably approximately the same; nor is there any difference in the mean values for those in whom the left lung was measured first as compared with those in whom the right lung was first measured.

Results

The results from these examinations may be seen in table 1, in which the percentage figures for the share of the right lung in the total lung capacity with its fractions are given, in addition to the quotient FRC/TLC and RV/TLC for both left and right lungs. The spirometrically obtained values for FRC/TLC and RV/TLC are also given in the table. By way of comparison, the results arrived at by Svanberg (2) in his examination of his healthy subjects in the recumbent position are also presented.

As appears from the table, there is good agreement between the mean values for the distribution of TLC and its fractions between the two lungs and those

TABLE 1

Bronchospirometric Determination of the Average Levels of the Different Lung Volumes in Supine Position in Healthy Subjects

Sex			TLC	VC	FRC	RV	FRC/TLC Per Cent			RV/TLC Per Cent		
			Per Cent Right				Right	Left	Spirometry	Right	Left	Spirometry
Male	Svanberg, 9 cases	Average	53	52	55	54	52	48	41	35	34	27
Male	Orinius and Ståhle, 8 cases	Average	52	52	53	53	40	39	40	22	22	22
		Ranges	49–55	49–55	45–61	46–60	26–54	20–58	23–56	9–35	10–34	12–31
Female	Svanberg, 11 cases	Average	53	53	55	55	55	52	43	40	39	29
Female	Orinius and Ståhle, 8 cases	Average	52	52	53	52	43	41	40	26	27	27
		Ranges	94–55	48–56	50–58	48–56	34–52	29–53	32–52	16–36	19–35	17–36

TLC—total lung capacity
VC—vital capacity
FRC—functional residual capacity
RV—residual volume

TABLE 2

RESULTS OF DETERMINATION OF THE DIFFERENT LUNG VOLUMES IN 8 HEALTHY MEN BY BRONCHOSPIROMETRY
The Values of FRC/TLC Found by Spirometry Are Also Given

Subjects	Age	Length	Weight	TLC		VC		FRC		RV		FRC/TLC Per Cent			RV/TLC Per Cent		
				Liters	Per Cent Right	Liters	Per Cent Right	Liters	Per Cent Right	Liters	Per Cent Right	Right	Left	Spirometry	Right	Left	Spirometry
	years	*cm.*	*kg.*														
T.H.	22	174	65	5.88	53	4.78	53	2.18	53	1.10	55	37	37	40	19	18	19
G.L.	25	190	81	8.43	53	6.23	52	3.59	53	2.20	54	43	42	41	27	25	25
R.W.	26	175	75	5.52	52	4.31	52	2.43	50	1.21	51	43	45	45	22	22	21
G.	26	177	64	5.95	52	4.25	52	2.98	54	1.70	55	51	49	46	30	27	25
P.K.	27	169	66	5.28	54	4.54	54	1.63	59	0.74	54	34	27	31	14	14	18
B.J.	27	172	82	7.79	52	6.07	51	2.57	57	1.72	57	36	30	32	24	20	20
G.K.	27	190	73	6.86	50	5.69	50	2.40	49	1.17	48	35	35	38	16	18	21
G.B.	33	173	70	6.85	52	4.96	53	3.01	50	1.89	49	42	46	46	26	29	29
M	27				52		52		53		53	40	39	40	22	22	22
E					0.4		0.4		1.2		1.1	2.0	2.8	2.1	2.0	1.8	1.3
σ					1.2		1.3		3.5		3.2	5.7	7.9	5.9	5.6	5.1	3.7
$M \pm 2.5 \times \sigma$					49–55		49–55		45–61		46–60	26–54	20–58	23–56	9–35	10–34	12–31

M = average or mean
E = epsilon, the standard deviation
σ = sigma, the standard deviation

TABLE 3

RESULTS OF DETERMINATION OF THE DIFFERENT LUNG VOLUMES IN 8 HEALTHY WOMEN BY BRONCHOSPIROMETRY

The Values of FRC/TLC and RV/TLC Found by Spirometry Are Also Given

Subjects	Age	Length	Weight	TLC		VC		FRC		RV		FRC/TLC Per Cent			RV/TLC Per Cent		
				Liters	Per Cent Right	Liters	Per Cent Right	Liters	Per Cent Right	Liters	Per Cent Right	Right	Left	Spirometry	Right	Left	Spirometry
	years	*cm.*	*kg.*														
I.H.	18	160	53	3.47	53	2.46	55	1.59	53	1.01	50	46	46	43	27	31	30
A.M.J.	18	169	60	4.66	53	3.60	53	1.70	55	1.06	51	38	35	34	23	24	20
B.J.	20	611	57	4.15	52	3.36	53	1.47	56	0.79	51	38	33	38	18	20	22
M.J.	20	168	56	4.24	50	3.03	49	1.91	50	1.21	50	46	44	44	29	28	27
G.B.J.	22	165	53	4.82	54	3.50	54	2.03	55	1.32	54	43	41	42	28	27	33
G.H.	22	178	65	4.83	52	3.57	52	2.17	54	1.26	52	46	43	42	26	26	28
T.P.	32	176	56	5.86	52	4.09	51	2.71	53	1.77	53	47	45	45	31	29	28
B.N.	36	161	66	5.20	52	3.82	52	2.02	53	1.38	52	40	38	35	26	27	28
M	24				52		52		54		52	43	41	40	26	27	27
E					0.4		0.7		0.7		0.6	1.4	1.7	1.5	1.4	1.2	1.5
σ					1.2		1.9		1.9		1.7	3.8	4.8	4.2	4.0	3.4	4.2
M $\pm$ 2.5 $\times$ σ					49–55		48–56		50–58		48–56	34–52	29–53	32–52	16–36	19–35	17–36
Pregnant in seventh month																	
A.S.	22	175	87	5.43	53	4.49	53	1.63	56	0.94	53	32	28	26	17	17	19

M = average or mean

E = epsilon, the standard error of the mean

σ = sigma, the standard deviation

communicated by Svanberg (2). Also Gaensler and Cugell (1) give an account of results of examination which tally for men.

With respect to the spirometrically obtained FRC/TLC and RV/TLC mean values, these show close agreement with the values for a larger group of subjects studied by Kaltreider and associates (7). In these studies FRC/TLC was 37 per cent and RV/TLC was 20 per cent for men (18 to 30 years, mean age 23 years); and 43 and 26 per cent, respectively, for women (18 to 34 years, mean age 23 years). With respect to FRC/TLC, Svanberg's figures also agree well with those in the present report; the agreement is less good, on the other hand, between his mean values for RV/TLC and Kaltreider's (7) and those in the present report. Svanberg's values are considerably higher.

In the present study the mean values obtained for FRC/TLC and RV/TLC with spirometry as well as bronchospirometry are very close to each other. This is in sharp contrast to what Svanberg (2) has found for his healthy subjects, for whom he reports a very considerably greater FRC/TLC and RV/TLC with bronchospirometry compared with spirometry (table 1). Svanberg explains this big difference as being due to the increased respiratory resistance with bronchospirometry. From what emerges from the present investigation, this explanation seems unacceptable, and the cause of this discrepancy in Svanberg's material must lie elsewhere.

This emerges too from Gaensler and Cugell's (1) investigation, in which, as in Svanberg's case, the nitrogen-elimination method has been used. They report for four healthy men a residual quotient of 20 per cent with spirometry and 20 and 21 per cent with bronchospirometry for the right and left sides, respectively. These values are thus close to those found in the present study, and there is no notable difference between the spirometric and bronchospirometric values.

With respect to FRC/TLC and RV/TLC for the left and right sides, these appear, as may be seen in table 1, to be practically equal for both sides, as was also found by Svanberg.

A healthy woman in the seventh month of pregnancy has been examined; a much lower quotient for both FRC/TLC, 26 per cent, and for RV/TLC, 19 per cent, was found.

Normal limits were set: mean $\pm$ 2.5 $\times$ standard deviation. The results of the examinations of the different experimental subjects are given in tables 2 and 3.

Summary

Eight healthy men and 8 healthy women have been spirometrically and bronchospirometrically examined, with simultaneous determination of functional residual capacity with the helium-dilution method, with special regard to the ratio residual volume (RV)/total lung capacity (TLC).

The normal values for this ratio have been found to be the following: for men, RV/TLC 22 per cent (mean value), limits (mean $\pm$ 2.5 $\times$ standard deviation) 12 to 31 per cent; for women, 27 per cent and 17 to 36 per cent, respectively.

On an average, the same values were obtained with both men and women for RV/TLC on examination of both right and left sides.

The mean value for RV/TLC was found to be the same with spirometry as with bronchospirometry.

Sumario

Determinación del Volumen Residual Bilateral. I. Examen de Sujetos Sanos

Ocho hombres sanos y 8 mujeres sanas fueron examinados espirométrica y broncospirométricamente, determinándose simultáneamente la capacidad funcional residual por el método de la dilución con helio, prestando atención especial a la proporción entre el volumen residual (VR) y la capacidad pulmonar total (CPT).

Los valores normales para dicha proporción resultaron ser los siguientes: para los hombres, VR/CPT 22 por ciento (cifra media), límites ($M \pm 2, 5 \times \sigma$) 12 a 31 por ciento; para las mujeres, 27 por ciento y 17 a 36 por ciento, respectivamente.

En conjunto, se obtuvieron los mismos valores de VR/CPT tanto para hombres como mujeres al examinar los lados derecho e izquierdo.

El valor medio de VR/CPT resultó idéntico con la espirometría y la broncospirometría.

Resume

Détermination du volume résiduel bilatéral. I. Examen d'individus normaux

Des examens bronchospirométriques et spirométriques ont été pratiqués chez 8 hommes et 8 femmes sains. La détermination de la capacité résiduelle par la méthode de dilution dans l'hélium en ce qui concerne particulièrement le rapport volume résiduel (RV)/capacité pulmonaire totale (TLC) a été effectuée simultanément.

On a enregistré pour ce rapport les valeurs normales suivantes: hommes, RV/TL 22 pour 100 (valeur moyenne), limites ($M \pm 2, 5 \times \sigma$) 12 à 31 pour 100; femmes, 27 pour 100 et 17 à 36 pour 100, respectivement.

En général, les mêmes valeurs pour RV/TLC ont été obtenues chez l'homme et chez la femme à l'examen des côtés droits et des côtés gauches.

La valeur moyenne de RV/TLC a été trouvée la même à la spirométrie et à la bronchospirométrie.

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DETERMINATION OF BILATERAL RESIDUAL VOLUME[1]

II. Examinations in Cases of Pulmonary Tuberculosis

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INTRODUCTION

Bronchospirometry with simultaneous determination of the functional residual capacity (FRC) for each lung separately has hitherto been performed only in a few cases of pulmonary disease. For a complete elucidation of the lung function, such an examination is necessary; otherwise the distribution between the two lungs of the functional residual capacity (FRC), the residual volume (RV), and the total lung capacity (TLC), as well as of the ratios FRC/TLC and RV/TLC, is not known.

For the determination of these lung volumes, FRC, RV, and TLC, two methods are available: the nitrogen-elimination method and the hydrogen- or helium-dilution method.

In 1934 Björkman (1) carried out a determination of functional residual capacity on each lung on 6 patients with pulmonary disease. He made use of an H_2-method in a closed system. In 1950 Frenckner (2) communicated the results of examinations in the case of workers with lungs which were affected after the inhalation of arsenic sulfur dioxide. There is no mention of the method employed or the number of cases. In 1952 Gaensler and Cugell (3) examined 16 patients with unilateral pulmonary tuberculosis with the nitrogen-elimination method. In 8 cases of minimal tuberculosis they found the vital capacity (VC) slightly reduced, while the residual volume was practically unchanged. In 8 severe cases of tuberculosis, on the other hand, the VC was markedly reduced, but the RV was only somewhat diminished. The remixing was delayed in the affected lung.

No bilateral determination of functional residual capacity with the helium-dilution method appears to have been published previously.

The aim of the present investigation has been to obtain bilateral determination of functional residual capacity as well as of the ratios FRC/TLC and RV/TLC for each lung separately. With these data it is possible to get an idea of the effect exercised on these ratios, especially RV/TLC, by different pathologic states and by surgical procedures in the course of pulmonary tuberculosis.

As the mean value for RV/TLC in a group of normal subjects is higher for women than for men (4, 5), the sexes have been treated separately. No distinction has been made between the left and right sides, however, because, according to the studies in normal subjects (4), as well as the studies of other investigators (3, 5), it has been found that no differences exist for these ratios, FRC/TLC and RV/TLC.

[1] From the Lung Physiology Department, Kolmarden Sanatorium, Sweden.

TABLE 1

COMPARISON BETWEEN AVERAGE VALUES OF FRC/TLC AND RV/TLC, FOUND BY SPIROMETRY AND BRONCHOSPIROMETRY

Sex	Distribution of Pulmonary Tuberculosis	Number of Cases	FRC/TLC		RV/TLC	
			Spirometry	Broncho-spirometry	Spirometry	Bronco-spirometry
			per cent	*per cent*	*per cent*	*per cent*
Male	Unilateral	11	45	44	30	26
	Bilateral	18	45	47	32	33
Female	Unilateral	11	44	44	28	29
	Bilateral	8	47	48	34	34

METHODS AND MATERIALS

Test objects: Twenty-nine men (aged 24 to 57 years, mean age 40 years) and 19 women (aged 21 to 44 years, mean age 33 years), all suffering from pulmonary tuberculosis, have been examined. In 11 men and 11 women the process was unilateral; the rest had bilateral changes. In the cases of 2 men and 4 women, a fresh examination was carried out three to four months after the performance of lung resection. Ten patients (6 men and 4 women) had been subjected previously to pneumothorax, in 3 cases (all men) bilaterally.

Methods: See Orinius and Ståhle (4).

Procedure: See Orinius and Ståhle (4).

RESULTS

In the present investigation the principal interest has been in the RV/TLC ratio. As may be seen from table 1, there is good agreement with respect to the mean values for the ratios FRC/TLC and RV/TLC resulting from both the spirometric and the bronchospirometric examinations. The same was the case in the studies of normal subjects (4).

A number of different factors may conceivably have caused changes in these values in the course of the pulmonary tuberculosis. The following five different factors were selected for study in this respect:

1. The occurrence of destroyed segments or lobes. As in practically all cases bronchography has been performed on the affected side or sides, it has been possible to make a clear diagnosis of such changes.
2. Spreading of the lung process over more than one lobe.
3. Previous collapse therapy. This has consisted of earlier pneumothorax treatment in 4 women and 5 men (in 3 bilaterally), and the same treatment was currently applied in one man.
4. The occurrence of extensive pleural thickening.
5. The occurrence of emphysema.

In addition to these five factors, a study has been made of the effect of the duration of the disease in connection with these factors.

In table 2 are given the mean values of FRC/TLC and RV/TLC for these factors. In this table no allowance has been made for the occurrence of more than one factor; if several factors have been present, the case has been reported under

TABLE 2

INFLUENCE OF DIFFERENT FACTORS IN PULMONARY TUBERCULOSIS ON THE RATIOS FRC/TLC AND RV/TLC (AVERAGE VALUES)

Sex	Male		Female	
Factors	FRC/TLC	RV/TLC	FRC/TLC	RV/TLC
1. Destroyed segments or lobes	46%	31%	48%	34%
	24 cases		14 cases	
2. Distribution, > 1 lobe	48%	35%	49%	34%
	13 cases		6 cases	
3. Earlier collapse treatment	53%	36%	48%	33%
	9 cases		4 cases	
4. Pleural thickening	51%	33%	50%	33%
	12 cases		3 cases	
5. Emphysema	48%	33%	49%	39%
	25 cases		4 cases	

TABLE 3

INFLUENCE OF DIFFERENT FACTORS IN PULMONARY TUBERCULOSIS ON THE RATIOS FRC/TLC AND RV/TLC (AVERAGE VALUES)

Only One Factor Existing in Each Case

Factor	Sex	FRC/TLC	RV/TLC
1. Destroyed segments or lobes	Male	40%	22%
		5 cases	
	Female	49%	32%
		6 cases	
5. Emphysema	Male	49%	33%
		4 cases	

each of these separately. As may be seen, the RV/TLC ratio in both men and women was considerably more than the mean value for the healthy subjects. For men, the ratio was relatively low for factor 1, while the value for factor 3 was definitely higher than for the others. For women, RV/TLC was pretty much the same for all factors except emphysema, in which a strikingly high value was found. The group comprises only 4 cases.

In table 3 the values are given for the cases in which only one of these five factors existed. It is only in the case of factor 1 for men and women and factor 5 for men that there has been a sufficient number of cases to afford a possibility of judgment. As may be seen, in the men there was a normal value for the factor "destroyed segments or lobes" and for women there was a slightly increased RV/TLC ratio. For the male emphysema cases (factor 5), the value shows good agreement with that given in table 2.

The values for FRC/TLC and RV/TLC are shown in table 4 in connection with the simultaneous occurrence of 0–5 of these factors. From this it appears clear that the occurrence of more than one of the factors mentioned, independent of which factors these may be, gives a considerable increase of the

TABLE 4

INFLUENCE OF COMBINATION OF FACTORS IN PULMONARY TUBERCULOSIS ON THE RATIOS FRC/TLC AND RV/TLC (AVERAGE VALUES)

Sex	Male		Female	
	FRC/TLC	RV/TLC	FRC/TLC	RV/TLC
5 factors	58% (3 cases)	35%	—	—
3 factors	44% (8 cases)	34%	48% (3 cases)	35%
2 factors	49% (16 cases)	35%	51% (6 cases)	37%
1 factor	44% (12 cases)	28%	45% (10 cases)	30%
0 factors	40% (8 cases)	24%	43% (8 cases)	29%

residual ratio; FRC/TLC as a rule is also increased. If none of these factors exist, practically normal values are obtained for FRC/TLC and RV/TLC.

The duration of the disease is a further factor of importance for the occurrence of an increased RV/TLC ratio. This relationship has been studied in table 5, in which the data for table 2 have been divided up into two groups for each factor, one with a duration of the disease of less than a year, and one with a known duration of more than one year. As appears from the table, the values that in this respect are obtainable from the relatively small material are considerably lower in cases in which the duration of the disease is "less than one year."

In the case of factor 5, emphysema, the age of the patient probably also plays a certain role for the occurrence of increased residual ratio. For men, the emphysema group has been studied from this standpoint (table 6.) As the table shows, this ratio is considerably higher for men more than 50 years of age.

A question of great theoretical, and sometimes even practical, importance is whether a spirometrically obtained residual ratio can reveal that the RV/TLC ratio for both the lungs is of approximately the same order of magnitude. This need by no means be the case, however, as is shown in figure 1.

Case 2219. A 37-year-old male who had had right-sided pulmonary tuberculosis since 1942 was treated with pneumothorax from 1942–1948, with residual large exudative filling with secondary immobilization of lung and diaphragm. Spirometry gave a normal residual ratio of 26 per cent, but bronchospirometric determination of RV/TLC showed that on the left side the ratio was low (19 per cent) and for the right side, clearly pathologic, at 37 per cent.

Case 2459. A 39-year-old male had bilateral pleurisies with residual pleural thickening bilaterally in 1943. Since 1947 he has had bilateral parenchymal changes in the upper lobes, with considerably greater destruction of the lung parenchyma on the right side demonstrated bronchographically. Spirometry showed a clearly pathologic residual ratio of 37 per cent, but bronchospirometry gave a normal ratio on the left side (25 per cent) and a marked pathologic value on the right side (43 per cent).

Case 2293. A 39-year-old male had had bilateral pulmonary tuberculosis since 1951, was treated with pneumothorax on the left side for eleven months in 1952, with residual pleural thickening; and on the right side in 1953–1955 without residual pleural thickening. Spi-

TABLE 5

INFLUENCE OF DURATION OF PULMONARY TUBERCULOSIS ON THE RATIOS FRC/TLC AND RV/TLC (AVERAGE VALUES)

Factor	Sex	FRC/TLC		RV/TLC	
		Duration of Tuberculosis			
		<1 year	>1 year	<1 year	>1 year
1. Destroyed segments or lobes	Male	40% 3 cases	46% 21 cases	23% 3 cases	32% 21 cases
	Female	47% 7 cases	50% 7 cases	32% 7 cases	36% 7 cases
2. Distribution, >1 lobe	Male	—	48% 13 cases	—	35% 13 cases
	Female	49% 3 cases	51% 3 cases	27% 3 cases	40% 3 cases
3. Earlier collapse treatment	Male	—	53% 9 cases	—	36% 9 cases
	Female	—	48% 4 cases	—	33% 4 cases
4. Pleural thickening	Male	48% 1 case	51% 11 cases	27% 1 case	34% 11 cases
	Female	—	50% 3 cases	—	33% 3 cases
5. Emphysema	Male	—	48% 25 cases	—	33% 25 cases
	Female	—	49% 4 cases	—	39% 4 cases
6. 0 factor	Male	47% 2 cases	37% 6 cases	26% 2 cases	24% 6 cases
	Female	38% 2 cases	44% 6 cases	26% 2 cases	30% 6 cases

TABLE 6

INFLUENCE OF EMPHYSEMA ON THE RATIOS FRC/TLC AND RV/TLC
Importance of the Age of the Patients

Emphysema Male	FRC/TLC	RV/TLC
	per cent	*per cent*
<50 years 18 cases	47	32
>50 years 7 cases	49	37

rometry before the operation showed a clearly pathologic residual ratio of 35 per cent; bronchospirometry, a clearly pathologic ratio on the left side (40 per cent); while on the right side the ratio was considerably lower (31 per cent). After segmental resection (4 segments plus periosteolysis) on the left side, a renewed examination by spirometry three months after the operation showed an unchanged ratio (34 per cent). The distribution between the two lungs, on the other hand, was essentially different. The ratio for the right side was unchanged on the whole (30 per cent), while that on the left side was 51 per cent. There was

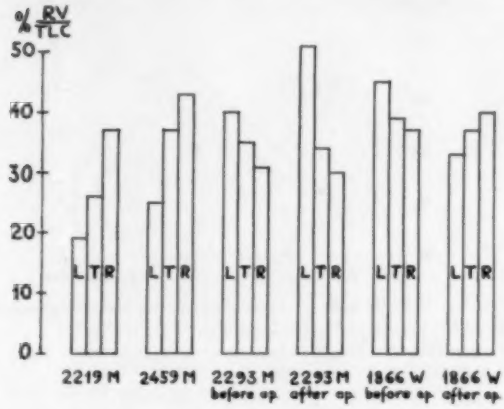

FIG. 1. Graph illustrating the partition of RV/TLC on both lungs, compared with the ratio, found on both lungs together (L = left, R = right, T = L + R).

an injury to the phrenic nerve in connection with the operation, which in the spirometric RV/TLC value gave no visible change, owing to the considerably reduced value for VC on the left side after the operation.

Case 1866. A 32-year-old female had bilateral pulmonary tuberculosis for less than one year, with extensive changes on the left side. Spirometry showed a clearly pathologic value for RV/TLC (39 per cent). Bronchospirometric determination of functional residual capacity gave a markedly pathologic value for RV/TLC on the left side (45 per cent) and also on the right side (37 per cent). After segmental resection (of three upper lobe segments plus periosteolysis) on the left side, spirometry performed three months later showed the same value for RV/TLC. Closer analysis, with determination of this ratio for each lung separately, showed that the RV/TLC ratio had been considerably improved on the operated side, to 33 per cent. This was within the upper calculated limit for healthy subjects, while for the right side the ratio had become still more pathologic (40 per cent). It was possible that a distension of the right lung might be present.

In 6 cases, 2 men and 4 women, bronchospirometry was performed before resection and three to four months thereafter. The results of these examinations may be seen in figures 2 to 7.

Case 2226 (figure 2). A 25-year-old female had had left-sided pulmonary tuberculosis since September, 1956. In March, 1957, a left-sided upper lobectomy and periosteolysis were performed. Roentgenographic examination three months later showed a very elevated diaphragm, which was less mobile than normally. Bronchospirometry was performed three months after operation.

Comment: On the operated side there was a very marked reduction of vital capacity (about 65 per cent), with unchanged residual volume, entailing a considerable increase of RV/TLC. This increase was conditioned chiefly by a much reduced diaphragmatic function. On the other side there was a distinct reduction of RV and RV/TLC, possibly due to a reduced distension of this lung.

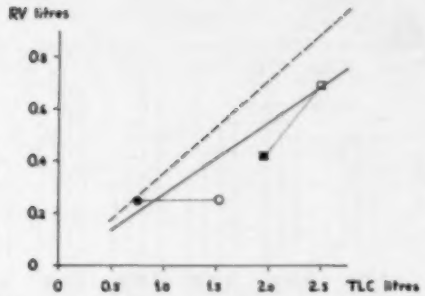

FIG. 2. Patient *No. 2226* (female). Graph illustrating the difference of the partition on both lungs of RV/TLC before and after lung resection (*see* text).
Left before operation ○ Right before operation □
after operation ● after operation ■
(Healthy subjects) RV/TLC ——— average value
(Healthy subjects) RV/TLC - - - - upper limit

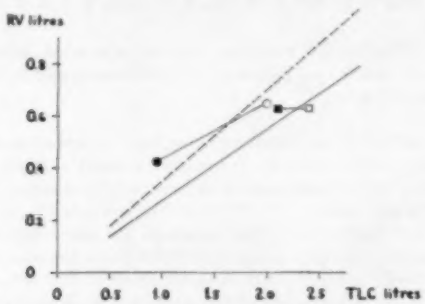

FIG. 3. Patient *No. 2284* (female). Graph illustrating the difference of the partition on both lungs of RV/TLC before and after lung resection (*see* text).
Left before operation ○ Right before operation □
after operation ● after operation ■
(Healthy subjects) RV/TLC ——— average value
(Healthy subjects) RV/TLC - - - - upper limit

Case 2284 (figure 3). A 24-year-old female had had left-sided pulmonary tuberculosis since October, 1956. In March, 1957, a left-sided upper lobectomy and resection of a subsegment of the apical segment of the lower lobe and periosteolysis were performed. Roentgenographic examination three months later showed a very elevated and rather fixed diaphragm on the operated side. Bronchospirometry was performed four months after operation.

Comment: On the operated side there was a very marked reduction of vital capacity (40 per cent) and a certain reduction of residual volume, resulting in a pronounced increase of RV/TLC (40 per cent) to a clearly pathologic value. This change seemed to be conditioned by the strongly reduced diaphragmatic function. The bronchospirometric values on the other side showed unchanged ratios on the whole.

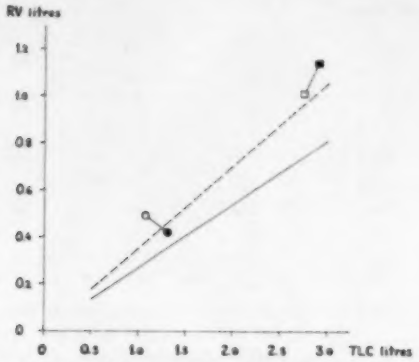

FIG. 4. Patient *No. 1866* (female). Graph illustrating the difference of the partition on both lungs of RV/TLC before and after lung resection (*see* text).
Left before operation ○ Right before operation □
after operation ● after operation ■
(Healthy subjects) RV/TLC ——— average value
(Healthy subjects) RV/TLC - - - - upper limit

Case 1866 (figure 4). A 32-year old female had had known bilateral pulmonary tuberculosis since January, 1956, with chiefly left-sided and very extensive changes. The process was undoubtedly, in part, of longer duration. In November, 1956, a resection of three upper lobe segments on the left side, together with a periosteolysis, was performed. Roentgenographic examination 3.5 months after the operation showed a high diaphragm which was fairly mobile. Bronchospirometry was performed three months after the operation.

Comment: On the operated side, even before the operation, there was a markedly reduced vital capacity (less than 0.6 liters) as well as a clearly pathologic value for RV/TLC. Postoperatively a clear increase of VC (40 per cent) occurred and there was a distinct improvement of the RV/TLC ratio with a value less than the upper normal limit. At operation a destroyed part of the lung with a large cavity was removed. On the other side, the VC was unchanged, but the RV/TLC ratio, clearly pathologic even before the operation, was increased thereafter. The probable cause of this was a distension of the lung, which was also indicated on the roentgenograms.

Case 2176 (figure 5). A 38-year-old female had had extensive bilateral tuberculosis of the upper lobes since her twenty-fifth year. She had emphysema bilaterally, more pronounced on the right side. In November, 1955, a right-sided upper lobectomy and resection of a subsegment of the apical lower lobe segment were performed. Roentgenographic examination three and a half months after the operation showed an elevated diaphragm which was nevertheless fairly mobile. Bronchospirometry was performed three months after the operation.

Comment: On the right side there was a marked reduction of vital capacity after the operation (50 per cent) with essentially unchanged residual volume, entailing a marked increase of RV/TLC (more than 50 per cent)—a clearly pathologic value. Increased distension of the previously emphysematous lung was probably a contributory cause. On the other side, too, there was a patho-

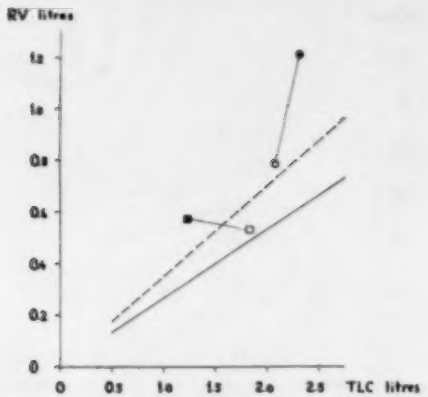

FIG. 5. Patient *No. 2176* (female). Graph illustrating the difference of the partition on both lungs of RV/TLC before and after lung resection (*see* text).
Left before operation ○ Right before operation □
after operation ● after operation ■
(Healthy subjects) RV/TLC ——— average value
(Healthy subjects) RV/TLC - - - - upper limit

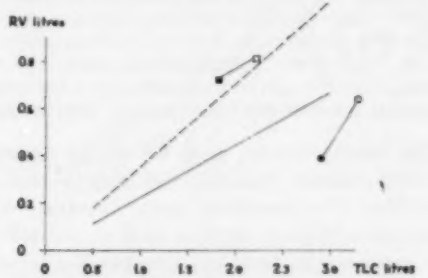

FIG. 6. Patient *No. 2219* (male). Graph illustrating the difference of the partition on both lungs of RV/TLC before and after lung resection (*see* text).
Left before operation ○ Right before operation □
after operation ● after operation ■
(Healthy subjects) RV/TLC ——— average value
(Healthy subjects) RV/TLC - - - - upper limit

logic RV/TLC value before the operation. This increased considerably after the operation (more than 30 per cent), which may have been caused by distension of this lung. The increase of VC (about 13 per cent) indicates that this might be the case.

Case 2219 (figure 6). A 37-year-old male had had right-sided pulmonary tuberculosis since 1942; he was treated with pneumothorax from 1942 to 1948 with residual large pleural thickening with secondary immobilization of the lung and diaphragm. In January, 1957, a right-sided decortication was performed. Roentgenographic examination three months after the operation showed a smoothed-out and laterally fixed diaphragm, which was fairly mobile. Bronchospirometry was performed three months after the operation.

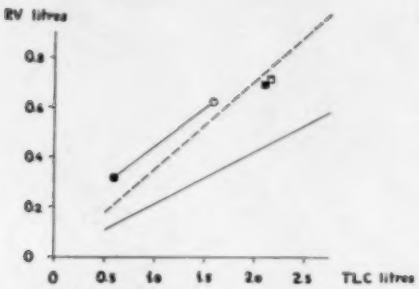

FIG. 7. Patient *No. 2293* (male). Graph illustrating the difference of the partition on both lungs of RV/TLC before and after lung resection (*see* text).
Left before operation ○ Right before operation □
after operation ● after operation ■
(Healthy subjects) RV/TLC ——— average value
(Healthy subjects) RV/TLC - - - - upper limit

Comment: On the operated side there was only a slight reduction of vital capacity (20 per cent) with a slight increase of the previously pathologic residual volume ratio. On the other side, there was a slight reduction of both vital capacity and residual volume, possibly supporting the assumption of a reduced distension on this side.

Case 2293 (figure 7). A 39-year-old male had had bilateral pulmonary tuberculosis since 1951. He had pneumothorax treatment on the left side for a short period in 1952 (eleven months), with residual pleural thickening, and on the right side from 1953 to 1955 without a residual pleural mantle. In March, 1957, a segmental resection (3 upper lobe segments and periosteolysis) was performed. In connection with the operation there was injury to the phrenic nerve. Roentgenographic examination three months after the operation showed the diaphragm on the left side to be still high and unmoving. Bronchospirometry was performed three and a half months after the operation.

Comment: The vital capacity on the left side, already reduced before the operation after pneumothorax treatment with secondary pleural thickening, was markedly reduced after the operation (70 per cent), owing to the injury to the phrenic nerve. The reduction of residual volume was relatively less, which entailed a certain increase of the preoperative pathologic RV/TLC ratio. On the other hand, all of the partial fractions of total lung capacity on the other side were unchanged. Roentgenographic examination after the operation showed the mediastinum to be in the normal position and there has been no distension.

DISCUSSION

Every pathologic state in the lungs has a certain effect on the lung function, either temporary or permanent. In the case of unilateral processes this applies as a rule only to the affected lung, but in cases of chronic pathologic condition, such as pulmonary tuberculosis, an injurious effect may also be obtained on the other side. Such an effect may result in displacement of the mediastinum and

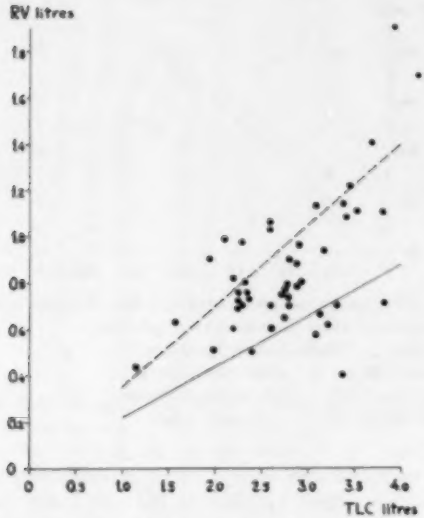

FIG. 8. Graph illustrating the partition of RV/TLC for the diseased lung in men (*see* text).
(Healthy subjects) ——— average value RV/TLC
(Healthy subjects) - - - - upper limit RV/TLC

distension of the other lung, with a certain risk of emphysema. Thus, with unilateral, as with bilateral, pulmonary tuberculosis, it should be considered a highly desirable determination of the function of both lungs.

With spirometry and bronchospirometry it is possible to diagnose a ventilation insufficiency as well as a quantitative parenchymal insufficiency of the lungs. On the other hand, these examinations reveal little concerning the occurrence of qualitative parenchymal (diffusion injury) or vascular pulmonary insufficiency.

A survey of the RV/TLC ratio in relation to normal values is given in figures 8 and 9 for men and women, respectively. As may be seen, nearly all of these values for RV/TLC are above the mean for healthy subjects and in several cases are near or above the calculated upper limit for this mean. The conclusion may be drawn from this that in most cases a tuberculous change in a lung entails an increase of RV/TLC for this lung.

All the examinations showing a RV/TLC at or under the mean value for normal subjects have been carried out in cases in which only one or none of the factors studied with respect to the effect on the RV/TLC ratio has been present.

Different factors or combinations of factors play a varied role for the occurrence of an increased RV/TLC ratio, and this is illustrated by tables 2 through 6. The factors causing an increased RV/TLC ratio that have been studied are: destroyed segments or lobes; the extension and duration of the lung process; earlier collapse therapy; pleural thickenings after pneumothorax treatment or

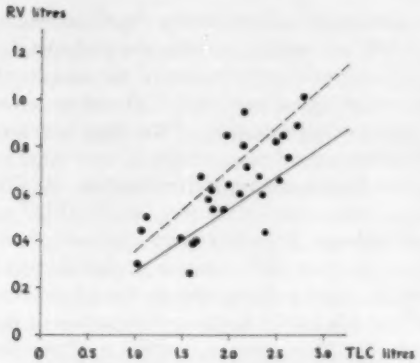

FIG. 9. Graph illustrating the partition of RV/TLC for the diseased lung in women (*see* text).
(Healthy subjects) ——— average value RV/TLC
(Healthy subjects) - - - - upper limit RV/TLC

pleurisies; and emphysema. In connection with the last-named, the significance of the patient's age has been studied as an RV/TLC-increasing factor.

It appears from table 4 that the occurrence of more than one of the above-mentioned factors as a rule entails a considerable increase of the residual volume ratio. Of these factors, "destroyed segments or lobes" appear to play a rather inconsiderable role (*see* table 3). This is not surprising, since these lung areas are generally more or less disconnected from the lung function through bronchostenoses. In one case, for example, there was a complete destruction of the whole of the upper lobe as well as the apical lower lobe segment on the right side; yet, despite this, RV/TLC on this side was only 30 per cent as against the normal value of 27 per cent for women.

On the whole, the other factors appear to be on a par as causes of increased RV/TLC. The more extensive pleural thickenings after pneumothorax and pleurisies seem to cause a considerable increase of RV/TLC.

The duration of the disease (*see* table 5), is also of importance. On an average, when it has lasted for more than one year, a definitely higher value is obtained for the different factors. For the role of emphysema as a factor increasing RV/TLC, the age of the patient is very important (*see* table 6).

When none of the above-mentioned factors enter, the RV/TLC ratio is as a rule rather normal, even in cases of a longer duration of the disease (*see* tables 4 and 5).

From a spirometrically obtained residual volume ratio, nothing definite can be said concerning the RV/TLC ratios of the two lungs taken separately, whether it is a matter of a unilateral or a bilateral lung process. As appears from figure 1, a clearly pathologic value for one lung may be concealed behind a spirometrically obtained, fully normal value for RV/TLC. Even in the case of apparently the same preoperative and postoperative spirometric values for RV/

TLC, occasionally there may be concealed a clearly increased RV/TLC ratio on the operated side, while on another occasion the postoperative value may be reduced (figure 1). For a complete elucidation of the lung function, bilateral determination of functional residual capacity is therefore necessary, especially in preoperative and postoperative studies of the lung function.

Six cases have been examined preoperatively and three to four months postoperatively with bronchospirometric determination of FRC (figures 2–7). A reduction of vital capacity and an increase of RV/TLC on the operated side have been the usual findings. The chief factors connected with the occurrence of these changes appear to have been fixation of the diaphragm through pleural thickenings not yet resorbed and injuries to the phrenic nerve. A certain role has probably also been played by a reduced excursion of thorax and diaphragm conditioned by pain. Doubtless, too, a distension of the lung-tissue postoperatively has played a role in a number of cases, since, apart from periosteolysis in 4 cases, no space-reducing operation has been performed. A bronchospirometric examination only three months after a resection gives, however, very little idea of the final lung function. This can only be assessed through such an examination performed at least one year after the operation.

In a large number of cases spirometry was done two to three weeks after resection, and in nearly all cases a markedly increased RV/TLC ratio was found. Moreover, as a rule, the vital capacity was not appreciably higher than the preoperative value for the nonoperated lung.

For the latest group of patients examined in this way (14 men), the postoperative mean value for vital capacity is only 0.5 liters higher than the preoperative value for the nonoperated lung (2.9 and 2.4 liters, respectively). The mean value for RV/TLC increased from 27.5 per cent before the operation to 37.5 per cent afterward. This supports the assumption that, to a great extent, the operated lung has no part in the lung function during the first postoperative period. In the majority of cases, this is probably chiefly due to a pain-fixation of the thorax and the diaphragm. If the patient is forced to use the lung on the operated side to manage his lung function, he will do this if it is possible. In selected cases one may very well perform segmental resections on the only functioning lung.

In the so-called healthy lung, a distension with increase of the RV/TLC ratio sometimes occurs. This is probably a passing stage in most cases; longer periods (more than one year) between operation and examination are required for a proper assessment. These preliminary figures cannot be taken as an argument in favor of always performing space-reducing operations in connection with lung resections.

As has already been mentioned, states of pulmonary insufficiency of vascular or diffusion type also probably have an effect upon the results of spirometric studies of the lung function. Because of this, one case not included in the material reviewed in the foregoing is deserving of more detailed mention. This refers to a woman thirty years of age, who had on either side a tuberculoma which was the size of a hazel-nut, with a small cavity on the right side. In addition to this, for several years she had had a mitral stenosis without signs of decompensation.

Preoperative bronchospirometry with bilateral determination of functional residual capacity showed clearly pathologic values for RV/TLC of 39 and 42 per cent, respectively, for the left and right sides without apparent cause. Bronchography showed normal bronchi, and at operation no emphysema could be shown on the operated side (right). The patient's oxygen saturation in the blood was 92 per cent according to Van Slyke; the blood pH was 7.47; the standard bicarbonate, 40 mM.; and the PCO_2, 60 mm. of mercury. This case presumably represents a diffusion injury connected with the heart disease.

In the present investigation of 48 cases of pulmonary tuberculosis, only those forms of pulmonary insufficiency have been considered that it has been possible to diagnose and follow with spirometry and bronchospirometry. It is recognized that in a number of these cases other forms of pulmonary insufficiency may have existed. The present investigation, however, has represented an attempt to fill a gap in the present knowledge of lung function from the spirometric-bronchospirometric viewpoint. The results so far obtained can only be regarded as preliminary, but it is hoped that within a year a sufficiently large amount of material may be available to enable a complete statistical assessment. In the future, it is planned to supplement these studies with a comparative investigation of functional residual capacity bronchospirometrically with the nitrogen-elimination and the helium-dilution methods.

Summary

In 48 cases of pulmonary tuberculosis the helium-dilution method has been used for determination of functional residual capacity bilaterally in connection with bronchospirometry.

The following factors have been found to be of importance for the increase of the ratio residual volume (RV)/total lung capacity (TLC) in pulmonary tuberculosis: viz., an extension of the lung process over more than one lobe, earlier collapse treatment, extensive pleural thickening, emphysema, and a duration of the tuberculosis for more than one year. The occurrence of more than one of these factors nearly always results in a clear increase of RV/TLC.

In preoperative and postoperative studies of the lung function, nothing can be said solely on the basis of a spirometric examination of functional residual capacity concerning the distribution of RV/TLC between the lungs. For a complete assessment of the lung function, bilateral determination of functional residual capacity is necessary.

Six cases, in which bilateral determination of functional residual capacity was carried out before and three to four months after the resection of the lung, are described in detail.

Sumario

Determinación del Volumen Residual Bilateral. II. Exámenes en Casos de Tuberculosis Pulmonar

En 48 casos de tuberculosis pulmonar se usó el método de la dilución con helio para la determinación bilateral de la capacidad funcional residual en relación con la broncospirometría.

Los siguientes factores han resultado ser de importancia en el aumento de la proporción del volumen residual (VR) y la capacidad pulmonar total (CPT) en la tuberculosis pulmonar, a saber, difusión del proceso pulmonar a más de un lóbulo, colapsoterapia más temprana, extenso espesamiento pleural, enfisema y duración de la tuberculosis por más de un año. La existencia de más de uno de estos factores casi siempre da por resultado un aumento bien definido de la proporción VR/CPT.

En los estudios pre y postoperatorios de la función pulmonar, no cabe decir nada exclusivamente a base de un examen espirométrico de la capacidad funcional residual con respecto a la distribución de VR/CPT entre los dos pulmones. Para una valuación completa de la función pulmonar, es necesaria la determinación bilateral de la capacidad funcional residual.

Descríbense a fondo 6 casos, en los que se ejecutó la determinación bilateral de la capacidad funcional residual antes y de tres a cuatro meses después de la resección del pulmón.

Resume

Détermination du volume résiduel bilatéral. II. Examen de cas de tuberculose pulmonaire

Dans 48 cas de tuberculose pulmonaire, la méthode de dilution dans l'hélium a été utilisée pour la détermination de la capacité résiduelle fonctionnelle bilatérale en liaison avec la bronchospirométrie.

Les facteurs suivants ont été trouvés importants pour l'accroissement du rapport volume résiduel (RV)/capacité pulmonaire totale (TLC) en tuberculose pulmonaire; l'extension des lésions pulmonaire à plus d'un lobe, c.a.d. le collapsus antérieur, l'épaissement de la plèvre, l'emphysème et la durée de la tuberculose au-delà d'une année. L'intervention de l'un ou de plusieurs de ces facteurs produit presque constamment une augmentation nette de RV/TLC.

Dans l'exploration pré ou postopératoire de la fonction pulmonaire, aucune conclusion ne peut être faite uniquement sur la base de la détermination spirométrique de la capacité résiduelle fonctionnelle concernant la distribution de RV/TLC entre les poumons. Pour une évaluation complète de la fonction pulmonaire, la détermination bilatérale de la capacité résiduelle fonctionnelle est nécessaire.

Les auteurs décrivent en détail six cas dans lesquels la détermination bilatérale de la capacité fonctionnelle résiduelle a été effectuée avant l'exérèse pulmonaire et trois à quatre mois après.

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THE HEMATOLOGIC ADAPTATION OF PATIENTS WITH HYPOXIA DUE TO PULMONARY EMPHYSEMA[1,2]

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INTRODUCTION

Since polycythemia secondary to hypoxia occurring at high altitudes was first described, there has been intense interest in this phenomenon. Hurtado and associates (1, 2) and others (3) have studied extensively the adaptation to hypoxia in people residing at high altitudes. It would be expected that any disorder leading to prolonged hypoxia would be associated with the same degree of polycythemia which is produced by living at a comparable altitude. Wilson, Borden, and Ebert (4) have shown that patients with hypoxia due to emphysema do not respond as anticipated. While some develop polycythemia, the increase in hemoglobin concentration is inconstant and usually less than predicted. The following studies were performed to try to elucidate the mechanism for this lack of response.

MATERIAL AND METHODS

Sixteen patients with severe pulmonary emphysema, established by clinical and pulmonary function studies, and with an arterial oxygen saturation of 92 per cent or less, were selected. The age range of these patients was forty-one to sixty-eight years, with a mean of fifty-nine years. All received the regular hospital diet except for sodium restriction in those instances in which cardiac decompensation was manifest. Each patient was examined with reference to the sternal bone marrow, blood content of stool, urinalysis, electrocardiogram, and roentgenogram of the chest in an effort to exclude other primary disease which might make the patient undesirable for study. If infection or heart failure were present, the studies were delayed until maximal improvement had been achieved. The normal subjects consisted of 8 healthy young adult males.

The pulmonary function tests consisted of: the total and the one-second vital capacity, maximal breathing capacity, functional residual capacity, expiratory and inspiratory reserve capacity, residual alveolar nitrogen, the total lung capacity, and residual lung volume. The methods used were those described by Comroe and co-workers (5).

The arterial oxygen and carbon dioxide were determined by the manometric methods of Van Slyke and Neill (6). The pH of arterial blood was determined on a heparinized, anaerobic sample at 37°C. in a Cambridge Research Model pH meter immediately following the arterial puncture.

The hemoglobin was calculated from the arterial oxygen capacity, assuming that 1 gm. of hemoglobin combines with 1.34 ml. of oxygen. The erythrocyte counts were performed with pipettes certified by the U. S. Bureau of Standards, with duplicate dilutions and counts in each case. The hematocrits of venous blood were determined, using an anticoagulant consisting of 6 mg. of ammonium oxalate and 4 mg. of potassium oxalate per 5 ml.

[1] From the Medical and Radioisotope Services, Veterans Administration Hospital; and the Department of Medicine, University of Oklahoma, Oklahoma City, Oklahoma.

[2] Presented before the Medical Session, as part of *Section 1B*, at the annual meeting of the American Trudeau Society, Kansas City, Missouri, May 6, 1957.

of blood, in a Wintrobe hematocrit tube, with a relative centrifugal force of 2,515 × G for thirty minutes. These were not done in duplicate. The mean corpuscular hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin concentration were calculated according to Wintrobe (7). The reticulocyte preparations were stained by the dry method with brilliant cresyl blue and counterstained with Wright's stain. The reticulocyte count was expressed as percentage of erythrocytes.

The apparent chromium-51 half-life of the erythrocytes was determined by the radioactive chromate method of Johnson and associates (8) and was expressed as the per cent of radioactivity remaining on the seventh day of the test. The total blood volume was determined by auto transfusion of 10 ml. of the subjects' erythrocytes tagged with 150 microcuries of radioactive chromium-51. One milliliter of the tagged blood was diluted to one liter with 0.1 N HCl and served as the standard. Five-milliliter samples were taken at ten minutes and the following formula was used:

$$\frac{\text{(Net counts standard)(dilution standard)(ml. injected)}}{\text{(Net counts sample)}} = \text{blood volume in ml.}$$

The erythrocyte volume was calculated by multiplying the blood volume by the hematocrit × (0.925), and the plasma volume was calculated by multiplying the blood volume by one minus the hematocrit × (0.925), when (0.925) is the correction factor for plasma trapping in the hematocrit (9).

The rate of iron disappearance was determined by injecting 25 microcuries of radioactive iron citrate intravenously and collecting samples of venous blood at 10, 30, 60, 90, 120, and 150 minutes. These samples were counted in a scintillation well counter and the following formula was used:

$$\frac{\text{(Sample counts/minute/ml.)(100)}}{\text{(10 minute sample counts/minute/ml.)}} = \text{per cent of radioactivity remaining}$$

The per cent of radioactivity remaining was plotted on semi-logarithmic paper and the rate of disappearance in minutes was calculated.

The rate of iron reappearance was calculated in the following manner. First the per cent reappearance was calculated each day by the following formula:

$$\frac{\text{(Net counts/ml. day X) (hematocrit of 10-minute sample)} \times 100}{\text{(Net counts/ml. 10-minute sample) (hematocrit day X sample)}} = \text{per cent reappearance}$$

The per cent reappearance value was then plotted on semi-logarithmic paper and the day on which the curve approached 100 per cent was arbitrarily taken as the day of maximal reappearance.

The serum iron was determined by the method described by Peterson (10).

The plasma-iron turnover rate was calculated, using the formula:

$$\frac{0.693}{\frac{\text{Fe-59}}{\text{T1/2}}} \times \text{mg. serum-iron/ml.} \times \frac{\text{plasma volume (ml.)}}{\text{kg. body weight}} \times 60 \times 24$$

$$= \text{mg. iron/kg. body wt./day}$$

Results

The data are expressed in the tables as the mean, standard error of the mean, and one standard deviation; those in the text, as the mean plus or minus the standard error of the mean.

TABLE 1

PULMONARY FUNCTION DATA*

	Emphysema			Normal		
	Mean	Standard Error of Mean	Standard Deviation	Mean	Standard Error of Mean	Standard Deviation
Vital capacity, total, liters	2.17	± 0.09†	0.37	4.50	± 0.04	0.12
Vital capacity, 1-second, per cent	38.10	± 3.52†	14.10	90.30	± 1.40	3.90
Maximal breathing capacity, liters/minute	31.20	± 4.64†	18.60	134.00	± 4.80	13.60
Residual volume, liters	3.41	± 0.32	1.25			
Total lung capacity, liters	5.73	± 0.37	1.44			
Residual alveolar nitrogen, per cent of O_2 after 7 minutes	3.80	± 0.17	0.65			
Arterial O_2, per cent saturation	84.68	± 2.05	7.45			
Arterial CO_2, volumes per cent	55.88	± 1.86	8.19			
P CO_2, mm. of mercury	47.40	± 1.89	7.55			
Arterial pH	7.39	± 0				

* Values expressed as the mean, standard error of the mean, and one standard deviation.

† Statistically highly significant difference, $P < 0.001$.

The results of the *pulmonary function tests* are summarized in table 1. The total vital capacity of the emphysema patients was 2.17 ± 0.09 liters and that of the controls was 4.50 ± 0.04 liters; the one-second vital capacity being 38.1 ± 3.52 per cent and 90.3 ± 1.4 per cent, respectively. The maximal breathing capacity of the patients with emphysema was 31.2 ± 4.64 liters per minute as compared to 134.0 ± 4.8 of the controls. The differences of these values are statistically significant with a probability value of 0.001. The remainder of the tests were performed on the emphysema patients only and were as follows: residual lung volume, 3.41 ± 0.32 liters, total lung capacity, 5.73 ± 0.37 liters; residual alveolar nitrogen after seven minutes of breathing pure oxygen, 3.80 ± 0.17 per cent; arterial oxygen saturation, 84.68 ± 2.05 per cent; arterial carbon dioxide, 55.9 ± 1.86 volumes per cent; and pCO_2 of arterial blood, 47.4 ± 1.89 mm. of mercury. The arterial blood pH was 7.39 ± 0.0.

The *hematologic data* for both groups of subjects are listed in table 2. The hematocrits of the emphysema patients revealed a mean value of 54.1 ± 1.46 per cent compared with that of the controls of 47.5 ± 1.50 per cent. This difference has a P value of <0.01. The mean erythrocyte count was 5.27 ± 0.14 million for the emphysema group and 5.27 ± 0.10 million for the normal group; and the mean hemoglobin values were 16.81 ± 0.30 gm. per 100 ml. and 16.4 ± 0.40 gm. per 100 ml., respectively. The mean corpuscular volume for the study group was 103 ± 1.49 cu. microns in contrast to the control group of 88.8 ± 1.3 cu. microns; the difference is significant statistically with a P value of <0.001. The mean corpuscular hemoglobin concentration values were significant to the same degree, being 31.2 ± 0.52 per cent for the study group and 34.9 ± 0.7 per cent for the control group. The mean corpuscular hemoglobin value

TABLE 2

HEMATOLOGIC DATA*

	Emphysema			Normal		
	Mean	Standard Error of Mean	Standard Deviation	Mean	Standard Error of Mean	Standard Deviation
Hematocrit †, per cent	54.0	± 1.46	5.63	47.50	± 1.50	4.20
Erythrocyte count, millions	5.27	± 0.14	0.55	5.27	± 0.10	0.30
Hemoglobin, gm. per 100 ml	16.81	± 0.30	1.13	16.40	± 0.40	1.20
Mean cell volume,‡ cu. microns	103.00	± 1.49	5.97	88.80	± 1.30	3.80
Mean cell hemoglobin, micromicrogram	32.10	± 0.55	2.20	30.50	± 0.60	1.80
Mean cell hemoglobin concentration,‡ gm. per ml. erythrocytes × 100	31.20	± 0.52	2.20	34.90	± 0.70	2.00
Reticulocyte count, per cent erythrocytes	0.95	± 0.10	0.37	0.78	± 0.20	0.50
Bone marrow-erythroid cells, per cent nucleated cells	21.50	± 3.40	12.70			

* Values expressed as the mean, standard error of the mean, and one standard deviation.
† Statistically significant difference, $P < 0.01$.
‡ Statistically significant difference, $P < 0.001$.

for the study group was 32.1 ± 0.55 micromicrograms and for the control group 30.5 ± 0.6 micromicrograms. The difference of these means was not statistically significant.

These indices show that the volume of the cell is increased with no actual increase in hemoglobin formation. Enumeration of reticulocytes revealed a mean value of 0.95 ± 0.10 per cent in the emphysema patients and 0.78 ± 0.20 per cent in the normal subjects. Examination of the sternal marrow of the emphysema patients revealed 21.5 ± 3.4 per cent of the nucleated cells to be of the erythroid series. This determination was not done on the normal subjects but this is within the range usually accepted as normal (7).

The *radioactive chromium studies* are summarized in table 3. The blood volume of 73.03 ± 5.96 ml. per kg. of the emphysema patients represents a 14 per cent increase over the 63.95 ± 2.30 ml. per kg. of the controls, but the difference is not statistically significant.

The erythrocyte volume of 36.05 ± 2.99 ml. per kg. for the emphysema patients compared to 27.90 ± 0.54 for the control group does not represent a statistically significant difference ($P = 0.05$ to 0.1). The relatively greater increase in erythrocyte volume as compared to total blood volume in the emphysema group can be accounted for by the increase in mean corpuscular volume. The plasma volumes of 36.98 ± 3.50 ml. per kg. and 36.06 ± 2.03 ml. per kg. for the study and control groups, respectively, revealed no difference. It should be noted that the plasma volume is dependent on the venous hematocrit and was not measured directly. The apparent radioactive chromium half-life expressed as per cent of radioactivity remaining on the seventh day was 81.20 ± 1.16 per cent for the emphysema group and 81.70 ± 0.53 per cent for the normal subjects.

TABLE 3

RADIOACTIVE CHROMIUM STUDIES*

	Emphysema			Normal		
	Mean	Standard Error of Mean	Standard Deviation	Mean	Standard Error of Mean	Standard Deviation
Total blood volume, ml./kg.	73.03	± 5.96	23.83	63.95	± 2.30	6.49
Erythrocyte volume, ml./kg.	36.05	± 2.99	12.00	27.90	± 0.54	1.50
Plasma volume, ml./kg.	36.98	± 3.50	14.00	36.06	± 2.03	5.74
Apparent chromium half-life, per cent radioactivity on seventh day	81.20	± 1.16	4.50	81.70	± 0.53	1.51

* Values expressed as the mean, standard error of the mean, and one standard deviation.

TABLE 4

RADIOACTIVE IRON STUDIES*

	Emphysema			Normal		
	Mean	Standard Error of Mean	Standard Deviation	Mean	Standard Error of Mean	Standard Deviation
Serum iron, γ per 100 ml.	129.1	± 12.2	48.7	89.4	± 7.5	21.1
Disappearance half-time, minutes	73.4	± 11.7	43.8	74.0	± 2.9	8.20
Maximal reappearance time, days	5.3	± 0.6	2.0	6.4	± 0.2	0.50
Plasma iron turnover, mg./kg./day	1.08	± 0.26	0.91	0.48	± 0.07	0.18

* Values expressed as the mean, standard error of the mean, and one standard deviation.

The *iron data* are summarized in table 4. The serum iron was 129.1 ± 12.2 γ per 100 ml. for the emphysema patients and 89.4 ± 7.5 γ per 100 ml. for the normal subjects. This difference is statistically significant ($P < 0.05$). The mean half-time of disappearance and mean maximal reappearance time showed no significant difference. It should be noted that the standard deviation of the half-time of disappearance, 73.4 ± 43.8 minutes, is large. It is possible that the short disappearance half-time observed in a few patients could have been due to iron deficiency or infection; however the correlation between the serum iron values and the disappearance half-time values within the study group ($r = 0.336$; $N = 12$) was not significant ($P > 0.05$). The plasma iron turnover was 1.08 ± 0.26 mg. per kg. per day in the emphysema patients and 0.48 ± 0.07 mg. per kg. per day in the control subjects. This difference is likewise not statistically significant ($P > 0.1$).

DISCUSSION

None of the patients in the study group developed a hemoglobin concentration consistent with the degree of oxygen unsaturation (figure 1). This is evidenced by the absence of a significant increase in hemoglobin concentration, reticulocyte counts, erythroid activity of the marrow, erythrocyte volume, and plasma-iron turnover. In contrast, normal residents at high altitude with a comparable oxygen saturation develop a substantial increase in all of these indices (2, 3, 11). It may be noted in figure 1 that a linear correlation exists between oxy-

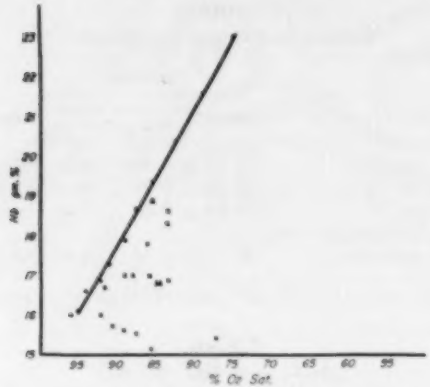

FIG. 1. The line joining the dots is constructed from data gathered from previous reports of the hemoglobin concentration in residents of high altitudes (1). Each *X* represents one of the patients in the present study. The *M* indicates the mean. If the patients responded as expected, the values should have distributed in a random fashion about the line.

gen saturation and hemoglobin concentration in persons at altitude; however, in this group of patients, although a negative correlation exists, the degree of correlation is not significant ($r = -0.166$, $N = 16$). This is in agreement with the previous studies of Wilson and associates (4) and Ratto and associates (12). The latter writers state that a hematocrit greater than 55 per cent and a hemoglobin concentration greater than 16.5 gm. per 100 ml. were rare in their group of patients with emphysema.

Several mechanisms for this lack of response to the hypoxic stimulus may be postulated. The plasma volume may be disproportionately increased and manifested by an apparently low hemoglobin and hematocrit of the peripheral blood. In this study, the plasma volume was not determined directly; hence, the data do not exclude this possibility although they make it seem unlikely. The production of erythrocytes could be normal with an increased rate of hemolysis. The values for the apparent radioactive chromium half-life of the erythrocytes show that these cells have a normal lifespan. The bone marrow may fail to respond to the stimulus resulting from hypoxia. This marrow unresponsiveness has been attributed to the chronic infection which patients with emphysema often have (4). That this may be a factor cannot be denied; however, Bush and co-workers (13) and Cartwright and Wintrobe (14) have characterized the anemia of infection as one in which the serum iron is decreased, the rate of disappearance of injected radioactive iron is rapid, the lifespan of the erythrocyte is shortened, the mean corpuscular volume is normal or decreased, and the bone marrow response is markedly impaired. It is apparent that these data are at variance with those of the anemia of infection, with the exception of the impaired marrow response. This suggests that, although infection may be contributory, it is not the sole etiologic factor.

Carbon dioxide retention has been submitted as a possible reason for this lack of response to hypoxia. Wilson and associates (4) were unable to show a relationship between carbon dioxide content and hemoglobin concentration, even when the effect of hypoxia was excluded by the method of partial correlation. The data of the present writers support this observation ($r = 0.153$; $N = 16$. $P > 0.05$).

Many of these patients have been followed for more than a year with no further increase in hemoglobin, so that the duration of hypoxia would not appear to be a factor. This confirms the observations of Wilson and associates (4).

It has been postulated that a humoral substance mediates the hypoxic stimulus (15, 16). Merino (17) has shown that 250 to 300 ml. of plasma harvested from residents at an altitude of 12,800 to 14,900 feet will induce an increase in reticulocytes of 0.80 ± 0.11 per cent when injected into normal recipients at sea level. It might be presumed that patients with emphysema have a defect in this mechanism, although evidence regarding this point has not been published.

Summary

Sixteen patients with pulmonary emphysema and arterial oxygen saturation below 92 per cent were studied. None of these patients developed the expected hemoglobin concentration for this degree of hypoxia. There was no significant difference between these patients and 8 normal control subjects in regard to blood volume, erythrocyte volume, reticulocyte count, hemoglobin, or iron turnover. The mean corpuscular volume was increased and the mean corpuscular hemoglobin concentration was decreased. It is notable that these findings are at variance with those described for the anemia of infection, although the evidence does support the concept of bone-marrow arrest. A defect in the humoral mechanism mediating the hypoxic stimulus may exist.

Sumario

La Adaptación Hematológica de los Enfermos con Hipoxia Debida a Enfisema Pulmonar

Este estudio comprende a 16 enfermos con enfisema pulmonar y saturación arterial de menos de 92 por ciento con oxígeno. Ninguno de estos enfermos manifestó la concentración de hemoglobina esperada para hipoxia de dicha intensidad. No hubo mayor diferencia entre estos sujetos y 8 testigos normales con respecto a volumen sanguíneo, volumen de eritrocitos, fórmula reticulocítica, hemoglobina o cambio de hierro. El volumen globular medio aumentó y la concentración media de hemoglobina globular disminuyó. Es de notar que estos hallazgos discrepan de los descritos para la anemia debida a infección aunque los datos disponibles apoyan el conepto de un estacionamiento de la médula ósea. Tal vez exista un defecto del mecanismo humoral que interviene en el estímulo hipóxico.

Resume

L'adaptation hématologique des malades présentant une hypoxie due à l'emphysème pulmonaire

Seize patients atteints d'emphysème pulmonaire et dont la saturation artérielle en oxygène était inférieure à 92% ont été étudiés. Aucun de ces malades n'a eu une concentration d'hémoglobine prévisible pour ce degré d'hypoxie. Il n'y avait pas de différence significative entre ces malades et huit sujets témoins normaux à l'égard du volume sanguin,

du volume érythrocytaire, du nombre des réticulocytes, de l'hémoglobine ou de la conversion du fer. Le volume corpusculaire moyen était augmenté et la concentration moyenne de l'hémoglobine corpusculaire était diminuée. Il y a lieu de remarquer que ces résultats diffèrent de ceux décrits dans l'anémie des infections, bien que des signes évidents confirment la conception d'une inhibition de la moelle osseuse. Il est possible qu'il s'agisse d'une alteration du mécanisme humoral transmettant le stimulus hypoxique.

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THE TUBERCULIN SKIN REACTION IN ACTIVE PULMONARY TUBERCULOSIS[1]

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INTRODUCTION

The value of the tuberculin skin test in the diagnosis of pulmonary disease increases year by year as fewer persons are exposed to tuberculous infection. It therefore becomes more important to understand the limitations of the test to allow better application and use.

In general, no skin reaction to 1 mg. of Old Tuberculin (OT) or to 0.005 mg. of purified protein derivative (PPD) is believed to exclude the presence of active tuberculosis except in certain diseases or under certain circumstances (1). A tuberculin reaction signifies in general only that the person has been infected at some time with tubercle bacilli. Much has been written in an attempt to correlate activity of disease with the tuberculin reaction and also the type of reaction elicited in active disease (2). Palmer (3) has stated that specific sensitivity to 5 tuberculin units (0.0001 mg.)[3] is almost universally seen in persons ill with the disease and in those who have had the disease. Furcolow and associates (4) found that 99.6 per cent of 468 tuberculous patients had skin reactions to 0.0001 mg. or less of PPD and they found no patients who had complete anergy.

The present writers have noted several patients with complete anergy to commercial PPD and OT and have observed many patients who failed to react to low doses of PPD. It was in an attempt to further evaluate these observations that the present study was undertaken.

MATERIAL AND METHODS

The skin reaction to tuberculin is routinely tested in all patients admitted to the Ohio Tuberculosis Hospital. The intradermal injection of tuberculin, purified protein derivative,[4] is employed. The reactions are interpreted by measuring the area of induration produced by the test material; 5 mm. or more of induration is considered a reaction. Skin testing usually is initiated with first-strength PPD (0.00002 mg.), and higher concentrations —intermediate-strength PPD (0.0001 mg.), second-strength PPD (0.005 mg.), and OT, 1 mg.—are employed until a reaction is obtained or the patient is clearly a nonreactor.

In this study the records of 1,000 consecutively admitted patients were reviewed. From this group were selected those patients who demonstrated evidence of pulmonary disease on roentgenography and from whom tubercle bacilli were cultured at least once during their hospital stay. Of the cases reviewed, 624 patients met the criteria for inclusion in the study.

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[3] One tuberculin unit (TU) = 0.00002 mg.

[4] Manufactured by Merck Sharp and Dohme.

TABLE 1

SKIN REACTION TO TUBERCULIN IN TUBERCULOUS PATIENTS

Patients	First-Strength PPD (0.00002 mg.)		Intermediate PPD (0.0001 mg.)		Second-Strength PPD (0.005 mg.)	
	Reactors	Nonreactors	Reactors	Nonreactors	Reactors	Nonreactors
567	444	123	76	49	43	4
53			46	7	7	
4					4	
624	444	123 (21.7%)	122	54 (8.7%)	54	4 (0.6%)

RESULTS

The data on the skin reactions are presented in table 1. Of those patients who had first-strength PPD, 21.7 per cent failed to react to this test. Of those who were negative to first-strength PPD, or who were initially given intermediate-strength PPD, 8.7 per cent failed to react to the intermediate-strength dose. Four patients had positive reactions to second-strength PPD, but no other tests were recorded in the chart. Four patients failed to give a reaction to second-strength PPD (0.005 mg.) and to OT (1 mg.) on admission to the hospital.

DISCUSSION

In the present study, the primary interest has been in the use of tuberculin as a diagnostic test. Although it has been stated previously that skin reactions to low doses of tuberculin occur in patients ill with tuberculosis, in this group of 624 tuberculous patients, a tuberculin skin reaction would not have been obtained in 21.7 per cent of the patients had first-strength PPD been used alone. Eight per cent (50 patients) of the group would have been designated as non-reactors if second-strength PPD (0.005 mg.) had not been employed.

Nonspecific reactions have been reported using second-strength PPD (3), and some have recommended that this dosage not be employed as a diagnostic test. If this advice had been followed in the present series, however, 8.7 per cent of the patients would have had "tuberculin-negative tuberculosis" whereas, in actuality, only 0.6 per cent were found to be in this category.

Of the 4 patients who were nonreactors to all concentrations of PPD and OT, all had overwhelming infection and were moribund at the time of admission to the hospital. All of these patients became reactors within two months after institution of antituberculous therapy.

Palmer (3) and Furcolow and associates (4) employed a standard PPD in their studies. The failure of patients to respond to commercial PPD thus raises the question of the potency of these preparations even though they are supposedly standardized against PPD-standard (PPD-S). The tuberculin PPD-S is not generally available, and the clinician must rely upon results obtained with the commercial preparations. Thus, the results obtained with an unavailable product are of little help to the person interested in diagnosis rather than epidemiology.

If large enough doses of commercial PPD are utilized, a reaction can be obtained in the great majority of patients (99.4 per cent). A person under these circumstances cannot be considered to be a nonreactor to tuberculin and therefore free of tuberculosis, however, unless he fails to react to PPD (0.005 mg.) or OT (1 mg.). With the results of the present study, certainly second-strength PPD cannot be discarded as a diagnostic test simply because it may produce a nonspecific reaction. The latter possibility must be kept in mind, but it is difficult to decide how such reactions can be interpreted.

Summary

One thousand patients admitted consecutively to the Ohio Tuberculosis Hospital were skin-tested with commercial PPD. Of this number, 624 had evidence of pulmonary lesions roentgenographically and had at least one specimen of sputum or gastric washings positive for tubercle bacilli on culture. Of these proved tuberculous patients, 21.7 per cent failed to develop reactions to first-strength PPD (0.00002 mg.) and 8.7 per cent failed to react to intermediate-strength PPD. Four patients initially revealed complete anergy to second-strength PPD and OT, 1:100, but became reactors with improvement in their disease. These data indicate the necessity for the continued use of the higher doses of tuberculin in the diagnosis of pulmonary lesions.

Sumario

La Cutirreacción a la Tuberculina en la Tuberculosis Pulmonar Activa

Mil enfermos admitidos consecutivamente al Hospital de Tuberculosis de Ohio fueron comprobados cutáneamente con PPD comercial. De ese número, 624 tenían signos radiográficos de lesiones pulmonares y habían tenido a lo menos un ejemplar de esputo o un cultivo gástrico positivo para bacilos tuberculosos. De estos tuberculosos comprobados, 21.7 por ciento no manifestaron reacciones a la primera dilución (0.00002 mg.) de PPD y 8.7 por ciento no reaccionaron a la dilución intermedia de PPD. Cuatro enfermos revelaron al principio anergia total a la segunda dilución de PPD y a la T. A. al 1:100, pero se volvieron reactores al mejorar la enfermedad. Estos datos apoyan el uso continuo de las dosis más altas de tuberculina en el diagnóstico de las lesiones pulmonares.

Resume

Le test cutané à la tuberculine dans la tuberculose pulmonaire

Mille malades admis consécutivement au « Ohio Tuberculosis Hospital » ont été soumis au test cutané avec PPD. Parmi ce nombre, 624 présentaient des signes evidents de tuberculose pulmonaire sur les radiogrammes et ils avaient au moins un spécimen de crachat ou de liquide gastrique positif en culture pour le bacille tuberculeux. Parmi ces tuberculeux avérés, 21,7% n'ont pas présenté de réaction au PPD, *first strength* (0,00002 mg) et 8,7% n'ont pas réagit au PPD *intermediate strength*. Initialement, 4 malades ont présenté une anergie compléte au PPD *second strength*, et à la tuberculine de Koch à 1%, mais ils sont devenus allergiques à mesure que leur infection s'améliorait. D'après ces données l'usage continu de doses plus élevées de tuberculine dans le diagnostic des lésions pulmonaires est préconisé.

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TUBERCULOMA OF THE LUNG[1]

S. SOCHOCKY

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Introduction

There is still a difference of opinion of what type and what size of tuberculous lesion should be termed a tuberculoma. There are several tuberculous lesions, viz., Assmann's focus, Simon's focus, Ghon's focus, other solid rounded foci, and tuberculous bronchopneumonia, which are included under this name. The term tuberculoma is a descriptive one and, as it is first diagnosed on roentgenographic examination, it must be of sufficient size to be seen on the films. In this paper the term tuberculoma is applied to the round or oval lesion more than 0.5 cm. in diameter, of postprimary tuberculous origin with definite borders.

Materials and Methods

The material on which this study is based consists of patients admitted to this hospital between 1951–1955 from other sanatoriums who were treated here by wedge or segmental resection or by lobectomies.

Clinical history: There were 30 patients in this group, 21 female and 9 male, the youngest being sixteen and the oldest fifty-five years of age, the majority being between the ages of twenty and forty years.

Thirteen patients were discovered by mass roentgenography to have pulmonary tuberculosis; 12 were symptom free; and one admitted to being tired for the past few months. Four patients were known contacts of a person with infectious tuberculosis; one was examined because of pregnancy; one was a diabetic, which was discovered on routine roentgenography; and one patient gave a history of pleural effusion. Nine other patients complained of ill health, loss of appetite, tiredness, and cough, with occasional hemoptysis for a period of time ranging from nine to thirty-six months; one had been under medical treatment and observation for eight years. The patients were treated with bed rest, antituberculous chemotherapy, and minor collapse therapy, such as artificial pneumothorax and pneumoperitoneum. All of the patients received antituberculous chemotherapy for a variable period prior to operation. The 10 patients who had been unsuccessfully treated with minor collapse therapy received chemotherapy for twelve to twenty-four months and, because of the occasional discharge of tubercle bacilli in the sputum, they were treated surgically. The remaining 20 patients received antituberculous chemotherapy for three to six months. In 17 cases, the sputum was positive for tubercle bacilli by microscopy or culture.

Observations

Roentgenographic Findings

The postero-anterior and lateral films were obtained for every patient, but it was found that tomographic studies were essential for the study of the pathology of the tuberculoma. The important roentgenographic findings in this lesion are the calcium salts, the cavities, the satellite shadows, and the involvement of the draining bronchus. With respect to localization, 19 tuberculomas were situated in the right lung and 11 in the left lung.

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On tomography, tuberculomas were seen as rounded or oval areas of density with fairly regular borders, and they were either homogeneous or heterogeneous in density and varied in diameter from 0.5 to 4 cm. Lobulation in one or other of the poles was seen in 8 cases. Cavities appeared as translucent areas, were found in 10 cases, and were situated either centrally or eccentrically.

The thickness of the cavity wall varied on an average of 0.1 to 0.4 cm., depending on the situation of the cavity (whether central or in the periphery). No

TABLE 1

SEGMENTAL DISTRIBUTION

(*30 Cases*)

	Upper Lobe			Lower Lobe			Total
	Apical Segment	Posterior Segment	Apico-posterior Segment	Anterior Segment	Apical Segments	Other Segments	
Right lung.....	3	4	5	1	4	2	19
Left lung.....	2	3	2	1	3	0	11
Total	5	7	7	2	7	2	30

FIG. 1*A*. Fairly round density with calcification situated in the apical segment of the left upper lobe. The draining bronchus appears to be thickened.

fluid level was seen in any of the cavities. Calcification was seen in 15 cases and was either central, peripheral, or scattered in an irregular manner throughout the lesion. The density of calcification varied in degree from mild to dense, but never attained to the density usually seen in primary lesions. Typical Liesegan's concentric rings were absent.

Twenty-six patients appeared to have active disease on tomography, and 10 of these had cavitation. Eight had lobulations in one or the other of the poles, 5 showed eccentric extension from the calcified focus, and 3 had tonguelike progressions from the center which transgressed the capsular ring at several points. Satellite shadows lay close to the main lesion and were present in 24 cases, but were absent in 6. The draining bronchus had irregularly thickened walls in 11

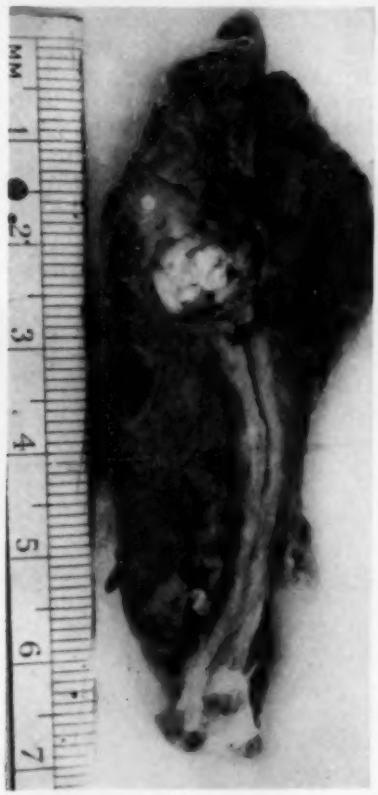

FIG. 1*B*. The lesion is cavitated at the infundibular end of the draining bronchus and is roughly 1 cm. in diameter. It contains firm, white, caseous, collagenizing material; the periphery is densely fibrous and contains minor foci. The apical bronchus is cylindrically stenosed from a point 1 cm. from its origin to its opening into the lesion. A narrow lumen remains.

cases, and in 3 of these there was an obliteration of the lumen of the bronchus, suggesting stenosis.

Pathologic Findings

Macroscopic examination: The size of the tuberculomas varied from 0.5 to 4 cm. in diameter and were either round or oval in shape; they were either homogeneous or heterogeneous in appearance, and were surrounded by normal lung tissue or minimal tuberculous disease. Cavitation was present in 10 cases, was either round or elongated in shape, and was situated in the center or toward the periphery, the cavity wall varying in thickness between 0.1 and 0.4 cm. Calcification was present in 15 cases and was distributed throughout the lesion, or was situated centrally or peripherally; and typical Liesegan's rings were seen in one case. Evidence of activity of the tuberculosis was seen as a cavitated extension of an old calcified focus in 5 cases, and as linear streaks expanding from the tuberculoma through the capsule toward the periphery in 3 cases. Satellite foci were present in 24 cases and were situated near the tuberculoma. The draining bronchus was thickened in 11 cases, in 5 of which bronchial stenosis was also present.

Microscopic examination: The histologic picture varied widely. In general, the foci were formed by: an outer layer of compressed lung, the so-called compression capsule; and an inner fibrous capsule, which varied in density and thickness depending upon the amount of fibrosis and hyalinization. Evidence of the char-

FIG. 24. Showing a "tennis racket" shadow situated in the apical segment of the left upper lobe. The draining bronchus is thickened.

FIG. 2*B*. A tuberculous focus of endobronchial origin has expanded by stenosis and ulceration of bronchial walls. The main bronchus has thickened walls, shows stenosis, and is very tuberculous.

acteristic cytologic activity of tuberculosis was almost always present in the capsule, being absent in only 3 of the 30 cases.

The degree of residual tuberculous capsule activity generally varied from slight to frank tuberculo-granulomatous. A central bulk containing the caseous material appeared white to gray in color, with or without calcium salts, and usually was interlaced by anthracotic fibrosed bands. If liquefaction and/or a cavity were present, it was usually irregular in outline. Calcium deposits occupied no constant site within the foci, and the pleural reactions overlying the focus included thickening edema and puckering.

Tubercle bacilli were found in only 22 of the 30 cases on direct microscopy of tissue sections.

The draining bronchus was thickened in 11 cases and was also stenosed in 5; of the 11 patients, 9 were tuberculous. In 6 cases the tuberculous draining bronchus was associated with cavitated tuberculomas and, in 3, the tuberculomas were of the "cold abscess of the bronchus" type (figure 2*A* and *B*). In 2 cases, the thickening of the bronchus was due to secondary changes on microscopic examination.

On roentgenographic and microscopic examination, tuberculomas of this series developed in one of four ways: in 15 cases there was a single progressive tuberculous focus; in 9, a circumscribed caseous pneumonia; in 5, a bronchial cold abscess, and in one case there was an encapsulated aggregation of small tubercles.

DISCUSSION

Opinion differs on the size of tuberculomas. Ritvo (1) applied the term to a round lesion or shadow of tuberculous origin, from a few millimeters to 8 or 10

cm. in diameter; some, i.e., Grenville-Mathers (2), have used the term tuberculoma to designate a lesion of 0.5 cm. in diameter; other writers (Hillerdal) have used the term for lesions of 1 to 2 cm. in diameter.

In the present series, the term was applied to a round tuberculous lesion of 0.5 cm. in diameter. With regard to the shape, all agree that a tuberculoma should be round or oval, with definite regular or irregular borders. The definite sharp outlines of tuberculomas were associated with a degree of hyalinized tissue in a fibrous capsular ring. This lesion occurs more often in female than in male patients, according to Hillerdal (3). In Berg's (4) series of 78 cases, 56 were women; in Sellors and Hickney's (5) series there were 27 females to 14 males; in Rüttman and Suter's series (6), the proportion of females to males was 3:2. In the present series there were 21 females to 9 males.

Most writers agree that tuberculomas are situated in the upper part of the lungs, in the intraclavicular regions, and more in the right lung than in the left. In the lower lobe, the tuberculomas are situated chiefly in the apical segment. Rüttman and Suter (6), in their series of 87 tuberculomas in 77 persons, show that 57 per cent of the lesions were in the lobes of the right lung, and 43 per cent in the left lung; and, of these, 69 per cent were in the upper lobes. Moyes, in his series of 41 cases (7), found 28 in the right lung and 13 in the left; and in 25 of these the lesions were found in both upper lobes.

Cavitations in tuberculomas are not uncommon, e.g., Hillerdal (3) found cavitation in 49 of 192 tuberculomas. In the present series, cavity was found in 10 of 30 cases. These cavities may contain a fluid level and are situated either centrally or closer toward the periphery; they may disappear and appear again, and a cavity of a tension type may also develop. That the cavitation may be seen in the malignant tumors of primary or of metastatic origin must also be recognized.

It is well known that the presence of the calcium deposits in the round lesions of the lung, as seen on roentgenograms, suggests either a tuberculoma or a tumor of a benign nature. Calcification may be found also in other benign lesions of lungs, as, for example, the hamartomas, old infarcts, abscesses, or in the walls of the cysts. Calcium deposits in hamartomas are usually distributed throughout the lesion in an irregular manner or are found mainly in the periphery, but are not arranged in concentric rings. The presence of the satellite shadows in the vicinity of the round lesion suggests its tuberculous origin. It should also be remembered that a bronchial carcinoma may develop in old round tuberculous calcified lesions.

Calcification was found in 15 of 30 cases in the present series and was distributed either throughout the lesion or situated centrally or in the periphery. No Liesegan's rings were found on roentgenographic examination, but they were found in one case on pathologic examination. Satellite shadows were found in 24 cases and were absent in 6 on tomograms and in the resected specimens.

The activity of a tuberculous lesion should be determined after taking into consideration all available information obtained or revealed by the clinical evidence and the laboratory and roentgenographic findings. The roentgenographic

findings are usually shown in rounded tuberculous lesions and increase in size, in the lobulation, and in the presence of a cavity. However, definite proof of activity could be assessed only in a series of roentgenograms which show whether the lesion is increasing, decreasing, or is stationary. On tomographic examination, 26 of 30 cases showed activity represented by: cavitation; an eccentric expansion from the center, in which a dense calcified focus was situated; lobulation, which was seen in the tuberculoma, due to a recent extension of disease; a tonguelike projection extending from the tuberculoma toward the periphery, at which point the capsule was transgressed by tuberculous granulation tissue. On microscopic examination, 27 cases showed activity, as demonstrated by the presence of tuberculous cytoactivity in capsular rings. Only in 3 cases was no such cytoactivity seen. In 22 cases, tubercle bacilli were found on microscopic examination of sections.

The question whether tuberculoma is of bronchogenic or hematogenous origin is still a matter of dispute. Hillerdal (3) thinks that it has a dual origin; according to Mahon and Forsee (8), the tuberculoma is a reinfection lesion by the aerogenous route. In the present series, the origin of the tuberculoma was bronchogenic in 27 cases and hematogenous in 3.

Opinion also differs with respect to the development of tuberculomas. The lesions are classified either according to roentgenographic or pathologic findings, or both. According to Moyes (7), the tuberculoma develops in three ways: as a postprimary caseous pneumonia, as an inspissated cavity, or as a primary focus. Hillerdal says it arises from a healing of cavities, from a bronchopneumonic lesion, or by confluence of small tuberculous bronchopneumonic foci—the latter by encapsulation. In the present series, the tuberculoma appeared to have developed either as: a single progressive tuberculous focus; a circumscribed caseous pneumonia; a bronchial cold abscess; or encapsulated aggregates of small tubercles.

As the tuberculomas are situated chiefly in the periphery of the lung, the bronchoscopies performed in this series were unrevealing. Tomograms, however, revealed the thickening of the draining bronchus in 11 of 30 cases. It was also stenosed in 3 cases. In resected specimens, the draining bronchus was thickened in 11 cases, and in 9 was due to the tuberculous process; in 2 cases the thickening of the bronchus was due to secondary changes on microscopic examination.

Reports of the finding of tubercle bacilli in the sputum of patients with tuberculomas have varied in different series. D. L. Pugh and associates (9), reported the sputum to be positive for tubercle bacilli in 3 of 28 cases of tuberculoma of the lung. In the present series the sputum was positive for tubercle bacilli on microscopy or on culture in 17 cases.

The diagnosis of the tuberculoma may be difficult, especially in middle-aged patients, because it resembles any bronchial or pulmonary disease which gives rise to a rounded circumscribed lesion on a roentgenogram of the chest. A family history of pulmonary tuberculosis or a history of contact is perhaps of some help. The physical examination is usually unrevealing, but the finding of tubercle bacilli in the sputum is of great help. Skin sensitivity tests, such as the Mantoux

reaction, may be useful, but this reaction may be negative in a patient with tuberculoma. The erythrocyte sedimentation rate is usually normal but may be elevated in active cases. Bronchograms were not done in the present series, but they may be of aid in localizing the involved bronchopulmonary segment and in excluding other pulmonary lesions such as a bronchial cyst. Bronchoscopy is usually normal in tuberculoma, but should be done in middle-aged patients to exclude malignant neoplasm. Tomograms, however, are essential in the presence of a discrete pulmonary lesion, for they show the size, shape, localization, cavitation, calcium salt, and satellite shadows, and the presumed activity or inactivity of tuberculosis if it be the cause of such a lesion.

All of the cases of tuberculoma in the present series were treated by wedge or segmental resection, or by lobectomy. There were no postoperative complications, and recent follow-up observations have shown no evidence of recurrence of disease.

Summary

Thirty cases of tuberculoma of the lung, occurring chiefly in patients between twenty and forty years of age, are reviewed. An account is given of the clinical history and roentgenographic and pathologic findings in this series of patients in an attempt to analyze the origin and development of tuberculomas.

Sumario

Tuberculoma del Pulmón

Repásanse 30 casos de tuberculoma pulmonar, observados principalmente en sujetos de treinta a cuarenta años de edad. Se ofrece una reseña de la historia clínica y de los hallazgos radiográficos e histopatológicos a la par que de la génesis y del desarrollo y del tratamiento prescrito.

Resume

Tuberculome du poumon

Trente cas de tuberculome du poumon, observés principalement chez des malades de 20 à 40 ans, sont analysés. L'histoire clinique, radiologique, ainsi que les résultats des examens anatomo-pathologiques, de même que l'origine et le développement et le traitement prescrit sont rapportés.

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EMPYEMA COMPLICATING PULMONARY TUBERCULOSIS[1]

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INTRODUCTION

The present study was prompted by the recent need at Manitoba Sanatorium to treat an increasing number of patients with empyema complicating pulmonary tuberculosis. Altogether, 44 patients with empyema were treated in the interval January 1, 1953, to March 31, 1957. During this period long-term antimicrobial therapy, as well as surgery, was available to all patients. Most of the surgical patients had chemotherapy for six months before operation. It should be stated at once that, although resection is now the main cause of empyema, a good many cases still arise from old pneumothoraces and a few from simple extension of gross pulmonary tuberculosis (table 1*A*). Thus, of the 44 patients with empyema, the disease in 25 followed resection (21 of the resections were performed in this sanatorium, and 4, elsewhere). Thirteen empyemas complicated pneumothorax and six were of the simple extension variety.

Tubercle bacilli were present in 25 of the 44 empyemas but frequently were not present in pure culture; in 16 instances other organisms, mainly staphylococci, were also present. In this series, for purposes of convenience, such "mixed" empyemas and the solely tuberculous variety are grouped under the one heading "tuberculous." In actuality, all of the 10 post-resection tuberculous empyemas were mixed, as opposed to 5 of the 9 following pneumothorax and only one of the 6 which were simple empyemas. Im empyemas in which tubercle bacilli were not found, staphylococci were the predominant offending microorganisms, and these empyemas have all been classified as staphylococcal.

In the present series, 10 of the 25 empyemas that followed surgical resection were classified as tuberculous, and 15 as staphylococcal. In the 13 that occurred after pneumothorax, 9 were tuberculous, 4 were staphylococcal, and all of the spontaneous empyemas were tuberculous. The bacteriologic type of infection had a distinct bearing on mode of development and response to treatment of empyemas. This point has not been sufficiently emphasized in the current literature and will be developed later in the present report.

The purpose of the study was twofold. The first was to gain a more thorough knowledge of causation in post-resection empyema. Analysis of cause was limited solely to this type of empyema as being currently the most common and amenable to prevention. Second, by appraising the present empyema treatment, it was hoped to gain a clearer concept of therapeutic principles and their application, not only in treating empyema following resection, but also in the empyemas arising from other causes.

[1] From Manitoba Sanatorium, Ninette, Manitoba, Canada.

TABLE 1*A*

EMPYEMA COMPLICATING PULMONARY TUBERCULOSIS, MANITOBA SANATORIUM
January 1, 1953–March 31, 1957

Type of Empyema	Tuberculous	Staphylococcal	Total
Post-resection	10	15	25
Post-pneumothorax	9	4	13
Spontaneous	6	0	6
Total	25	19	44

OBSERVATIONS

Etiologic Factors in Post-Resection Empyema

During the study period, 342 thoracotomies were performed on 322 patients. The group was analyzed in detail in a search for causative factors in post-resection empyema. These were divided into basic and local factors.

Basic factors: The analysis revealed four factors of a general nature that appeared to be significant. These have been designated as basic and are as follows: relapse, chronicity, persistence of tubercle bacilli in the sputum before surgery, and ineffective antituberculous chemotherapy in association with surgery.

In table 1*B* it may be seen that empyema was common in patients whose disease underwent a relapse or was generally chronic. Thus, 4 of the 6 tuberculous empyemas and 9 of the 13 staphylococcal empyemas occurred in patients who were being treated for a relapse of their pulmonary tuberculosis. With respect to chronicity, all patients developing post-resection empyema had had their tuberculous disease for two years or more. Conversely, no patient in this series with tuberculosis less than two years old developed empyema. As might be expected, patients developing tuberculous empyema usually have infectious sputum before surgery, and such was the case in 5 of the 6 in the present series. Even more striking was the adverse effect of drug-resistant strains of tubercle bacilli. Thus, in all patients who developed tuberculous empyema, various antituberculous drugs had apparently become ineffectual. All 7 of these patients had had chemotherapy for at least one year, and 4 had drug treatment for more than two years before the empyema. In all cases this comprised the use of regimens including the three drugs, streptomycin, PAS, and isoniazid, at one time or another. As will be seen, staphylococcal empyema was twice as frequent in patients whose sputum continued to contain tubercle bacilli resistant to antituberculous drugs. Long-term preoperative chemotherapy was not as common in patients developing staphylococcal as tuberculous empyema, although all but 2 of the 13 with staphylococcal empyema had been receiving tuberculous chemotherapy for six months or more.

Local factors: It has been generally believed in the past, certainly before the advent of antimicrobial drugs, that endobronchial disease at the site of bronchial resection was a significant local factor in the development of tuberculous empyema. The findings in the present series do not bear this out. All patients were

bronchoscoped routinely, and tuberculous endobronchitis was not an uncommon finding during the early stages of treatment. However, none of the 6 patients who developed tuberculous empyema postoperatively showed evidence of active endobronchial tuberculosis before surgery. Actually, good clearing of endobronchial disease, when present, took place in all but one patient. This patient represented a very hopeless case, and he died within twenty-four hours of operation, thereby precluding the development of any possible empyema. All patients with pneumonectomy in this series, besides showing good clearing of endobronchial disease, had routine thoracoplasty before coming to resection. In the opinion of the present writers, a space-reducing thoracoplasty is important in preventing empyema, but credit must obviously be given to antimicrobial therapy for the improvement in the endobronchial disease.

In table 1*B* may be seen the local factors considered significant, namely, difficulty in space obliteration, pleural space hemorrhage, staphylococcal wound infection, and tuberculous wound infection. Difficulty in space obliteration was encountered in approximately half of both the tuberculous and the staphylococcal empyemas, as compared with an incidence of 40 (11 per cent) in the 342 thoracotomies. Pleural space hemorrhage sufficient to diagnose by roentgenography and aspiration was relatively more common in those who developed empyema, especially staphylococcal, than in the group as a whole. Four of the 13 staphylococcal empyemas had this complication. Staphylococcal wound infection developed in approximately half of those with staphylococcal empyema, but was present in only 4 per cent of the whole series. Tuberculous wound infection was present in only 1.7 per cent of the whole series, but was found in two-thirds of those with tuberculous empyema. It is not clear why empyema and wound infection are so commonly associated. In the staphylococcal variety, the frequent involvement of both pleural space and chest wall tissues seems most likely to be

TABLE 1*B*

ETIOLOGY: POST-RESECTION EMPYEMA

January 1, 1953–March 31, 1957

Variables	Tuberculous Empyema—6		Staphylococcal Empyema—13		Total Series, 342	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Basic factors						
Relapse	4	66	9	69.2	133	39
Chronicity (disease present more than 2 years)	6	100	13	100	201	58.7
Sputum infectious before surgery	5	83.3	5	38.4	66	19.3
Ineffective antituberculous chemotherapy	6	100	5	38.4	52	15.2
Local associated factors						
Pleural space hemorrhage	1	16.6	4	30.8	23	6.7
Wound infection, staphylococcal	0	0	6	46.1	15	4.4
Wound infection, tuberculous	4	66.6	0	0	6	1.7
Difficulty in space obliteration	3	50	6	46	40	11

due to the patient's general lack of resistance to staphylococcal infection, of which more will be said later. In tuberculous infections, pleural and chest wall contamination must often occur concomitantly at operation when cutting across active tubercle-laden parenchymal tissue.

The significant findings in a study of the post-resection air spaces in the group are presented in table 2. The time of the appearance of the residual air space is considered of importance. Persisting air spaces are those present at once and persisting for more than two weeks postoperatively. Reappearing air spaces are those that recur after a period of days or weeks during which the space has been obliterated, either by lung re-expansion or postoperative opacity. Empyema developed in 5 of 28 patients with persisting air spaces, as against 14 of 26 with reappearing air spaces. Thus, empyema was about three times more common in reappearing than in persisting air spaces.

Recognition of this time relationship is of definite value in the management of post-resection air spaces. The significant difference between the two types is both anatomic and pathologic. Persisting air space is frequently due to the reduction in the expansibility of the remaining lung tissue from fibrosis and emphysema aided at times by a restricting coat of plastic exudate. The problem is one of anatomic disproportion between such a lung remnant and the pleural cavity. On the other hand, the reappearing air space is due to some added pathologic change. This may be relatively innocuous, as in the rupture of an emphysematous bulla, but is more often due to an active inflammatory process, either tuberculous or staphlyococcal, perhaps commencing in the lung parenchyma rather than in the pleura, and finally causing the opening of a bronchus through necrosis.

The presence of a bronchial communication is an important predisposing factor in empyema. Such a communication was present in 17 of the 19 post-resection empyemas in the present series and was most common in the reappearing air space group. An empyema of the reappearing air space type is frequently ushered in by sudden bronchial break-through with associated malaise, cough, wheeze, and bloody sputum. In the experience of the writers, a bronchial communication is always potentially dangerous in either persisting or reappearing spaces. Air spaces without bronchial communication tend to run a benign course whether treated actively or not. Many are present for several months before final obliteration. These closed air pockets are much more common in the persisting than in the reappearing air space group.

TABLE 2

ETIOLOGY: POST-RESECTION EMPYEMA

January 1, 1953–March 31, 1957

Type of Air Space	Infected Spaces				Sterile Spaces		Total
	Bronchial Communication		No Bronchial Communication		Bronchial Communication	No Bronchial Communication	
	Tuberculous	Staphylococcal	Tuberculous	Staphylococcal			
Persisting	1	3	—	1	1	22	28—18% infected
Reappearing	5	8	—	1	4	8	26—54% infected

The incidence of empyema in the whole series and in the various types of resection may be seen in table 3. In the total group of 342 thoracotomies, the incidence was 5.5 per cent, 1.7 per cent of which were tuberculous, and 3.8 per cent, staphylococcal. Thus, staphylococcal empyema was twice as common as

TABLE 3

ETIOLOGY: POST-RESECTION EMPYEMA

January 1, 1953–March 31, 1957

Type of Operation	Tuberculous Empyema—6		Staphylococcal Empyema—13		Total		Thoracoplasty	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Before	Space Reducing
156 wedge resections	1	0.6	2	1.3	3	1.9	2	4
16 segmental resections	0	0	0	0	0	0	0	3
22 combined resections	0	0	3	13.6	3	13.6	3	0
78 multiple resections	4	5.1	4	5.1	8	10.2	7	6
46 lobectomies	0	0	3	6.5	3	6.5	7	4
15 pneumonectomies	1	6.2	1	6.2	2	12.4	10	4
9 other types of resection	0	0	0	0	0	0	0	0
342 total	6	1.7	13	3.8	19	5.5		

TABLE 4

ETIOLOGY: POST-RESECTION EMPYEMA

January 1, 1953–March 31, 1957

Empyema Formulas

Type of Operation	Tuberculous Empyema—6		Staphylococcal Empyema—13		Total—19	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
156 wedge resections	1—CRDSH	0.6	2—CRSH CSW	1.3	3	1.9
16 segmental resections	0	0	0	0	0	0
22 combined resections	0	0	3—CRSH CR CRSI	13.6	3	13.6
78 multiple resections	4—CRPDW CPDSW CRPDSW CPDSW	5.1	4—CRSW CSW CPDSH CR	5.1	8	10.2
46 lobectomies	0	0	3—CRPDSH CPDI CRSH	6.5	3	6.5
15 pneumonectomies	1—CPDI	6.2	1—CRPDI	6.2	2	12.4
9 other types of resection	0	0	0	0	0	0
342 total	6	1.7	13	3.8	19	5.5

C—chronicity; R—relapse; P—positive preoperative; D—drug-resistant; S—space problem; H—pleural hemothorax; I—infection from without; W—associated wound infection.

tuberculous empyema. The incidence of empyema varied widely in the various types of resection performed, running from none in segmental resections to 13.6 per cent in cases in which a combined wedge and segmental technique was used. In table 4 is presented what has been termed the "formula" or pattern of each empyema occurring in the various types of resection. It will be seen that in all cases some combination of the basic and local associated factors already discussed was present. No case had less than two such factors, and in 15 of the 19 cases, 4 or more factors were present. It appears that empyema is related more to the disease status and the pathologic nature of the disease being treated, as determined by these factors, than to the type of operation performed. In other words, factors such as chronicity, drug resistance, persistently infectious sputum, space problems, pleural hemorrhage, and similar factors are more important as causes of empyema than whether the patient had a segmental or a wedge resection. This point will be further developed in the discussion.

Discussion

Causative factors will be discussed before consideration of the subject of treatment. In reviewing the literature on the etiology of empyema there seems less disagreement than difference in emphasis as to the causative factors involved. It appears that no two institutions are identical in the type of tuberculosis chosen for surgery, the surgical technique employed, and the postoperative management; and the opinions formed are no doubt an expression of this experience.

Hiltz and associates (1) in 500 consecutive resections have reported a higher incidence of empyema in patients with short-term preoperative antimicrobial therapy, especially with endobronchial disease. The incidence of empyema varied with the magnitude of the resection, being the highest in pneumonectomy. Douglas and associates (2), in 589 thoracotomies, reported tuberculous empyema only in the lobectomy groups, but it was more frequent in "desperate risk" than in elective surgery. Bell (3), in a series of three articles, dealt at length with the question of the post-resection space. Among his conclusions is an increasing conviction that thoracoplasty, either before, during, or after resection causes sufficient respiratory disability to offset its value as a safeguard against postoperative complications. Both Wareham (4) and Weisel (5) and their associates independently present evidence that residual air spaces, although potential hazards, are not necessarily followed by empyema. Thomas (6), in reporting 100 resections, predominantly elective in type and done in an army hospital by a cosmopolitan group of surgeons, stresses the human factor as accounting for one-third of the complications.

In the present experience, post-resection empyema is a complication which develops only in patients in whom the disease has unusual elements of chronicity. This applies to both tuberculous and staphylococcal empyema. It is believed that the explanation lies in the complexities of tuberculous pathology, well known to all, but sometimes overlooked as a determinant of the course of clinical disease.

It must be kept in mind that tuberculosis, although tending to be a chronic disease, does pass through an earlier pathologic phase in which the disease is

mainly exudative with perhaps some fresh cavitation; but fibrosis, pleural thickening, emphysema, and all the other manifestations of chronicity have not yet appeared. Patients who come to surgical treatment during this stage have an excellent chance of undergoing resection without developing empyema, always providing they have shown good clearing of exudation and reversal of infectiousness on adequate preoperative chemotherapy, i.e., around six months. Many patients fall into this class.

No such patient with early tuberculosis developed empyema following resection in the present series. It is believed that this reflects the fact that the lungs of such patients have not as yet lost their elasticity due to chronic disease. Hence the lung readily expands, and space problems are uncommon. However, in patients whose tuberculosis has already become chronic, the incidence of empyema was considerable. Tuberculous empyema in these chronically diseased patients almost always was due to cutting across tissue containing tubercle bacilli. Patients with more chronic disease who have responded well to drug therapy and no longer have tubercle bacilli in their lung tissue usually escape tuberculous empyema, but not uncommonly fall prey to the staphylococcal variety. For, the results of the chronic process—the fibrosis, emphysema, and pleural thickening, which makes these lungs poorly expansile and results in residual space problems—predispose to staphylococcal infection as well. These chronically diseased lungs often have damaged bronchial architecture, poor drainage, and associated nontuberculous bacterial infection, all of which may contribute to the development of staphylococcal empyema.

In the present series, tuberculous empyema did not develop following any of the lobectomies and occurred after one pneumonectomy. In the latter case, contamination took place in the course of dissecting through an already existing tuberculous empyema. Bronchial closure in all cases was made by simple over-end sutures of triple 0 silk. No re-enforcing sutures were used, and the stump was only rarely covered with pleura. For this reason it is believed that nothing in the technical management of the bronchial repair per se could be given credit for avoiding the development of empyema. It seems more likely that the bronchial repair held well due to the absence of active endobronchial disease, as demonstrated by preoperative bronchoscopy, as already mentioned. In addition, every attempt was made to avoid postoperative residual space, of which more will be said later.

In the opinion of the present writers the most fertile source of tuberculous empyema is transection of active tubercle-laden parenchymal disease tissue extending over lung unit borders. This occurred in 5 of the 6 tuberculous empyemas in the present series; once in wedge resection, and four times in multiple resection. Thus, the hazard seems greatest in multiple resection, the need for which is most often forced upon the surgeon in dealing with so-called "salvage" or "poor risk" cases. These patients usually are discharging drug-resistant tubercle bacilli in the sputum and have disease extending over lung unit borders. The surgeon is faced with a dilemma. Reduced breathing capacity may influence him to use multiple resection which courts disaster from empyema while conserving

much-needed lung tissue. Such resection at times ends badly, but on the other hand may succeed in rehabilitating an otherwise hopeless case. Perhaps the only way to avoid empyema in these cases is to deny resectional surgery and, when possible, to attempt extraperiosteal pack. Recently this has been done in some cases in this hospital and has been found to be safe, but the results were unimpressive.

The problem of residual space in large resections is of special interest to the present writers, in view of the peculiar nature of the experience in this regard. The incidence of tuberculous empyema has always been low at Ninette, even during the days of little or no chemotherapy when many writers were reporting relatively higher rates. Thus, during the period 1949 to 1952, in larger resections confined to one unit of lung tissue and comprising 14 pneumonectomies and 11 lobectomies, the incidence of tuberculous empyema was only 1 (4%), and there were no staphylococcal empyemas. In this group, 84 per cent of patients had tubercle bacilli in the sputum before surgery and 36 per cent had various degrees of endobronchial disease.

On the other hand, 80 per cent had the space-reducing benefit of thoracoplasty either before, during, or after resection. As pointed out in a previous report (7), the resections during this era were largely confined by circumstance to thoracoplasty failures so that space-reducing surgery was already present as a protection against empyema. Thoracoplasty is still used routinely in pneumonectomy but, in lobectomy, thoracoplasty is used in only one-third as many patients as formerly. However, it should be done when feasible in advance of lobectomy in all patients with drug-resistant infections. At the present time, most patients being in non-infectious status at the time of surgery, residual space is more often a factor in the development of staphylococcal than tuberculous empyema.

Staphylococcal empyema appears to be on the increase, with an incidence of 3.8 per cent in the present series. For reasons already mentioned, chronicity of tuberculous disease seems to favor staphylococcal as well as tuberculous empyema. The more frequent incidence of staphylococcal empyema in those with staphylococcal wound infection is not too easily explained. In 2 patients, the pleural space was contaminated at operation by dissecting through infected chest wall tissue. In the remaining 4, no interference took place that could carry infection from the chest wall to the pleural space, or vice versa. Pleural-space hemorrhage increases the risk of empyema, and blood clot favors especially the growth of the staphylococcus. However, chronic disease seems essential to this process. Thus, in the early years of this series and before a change in technique, hemorrhage occurred most commonly in resection of the residuum from small fresh lesions, but empyema failed to develop in any of these cases.

In review it will be seen that tuberculous and staphylococcal empyemas have common roots of origin, namely, the pathology present in chronic pulmonary tuberculosis. The factor determining which form develops is the presence or absence of tubercle bacilli in sputum and lung tissue at the time of surgery. Residual pleural space is a potent factor in the development of either tuberculous or staphylococcal empyema. Hemothorax predisposes in particular to staphylo-

coccal empyema. In present-day surgery, staphylococcal empyema is a much more common complication than the tuberculous variety and was found twice as frequently in the present series.

Empyemas are classified as post-resection, tuberculous, or staphylococcal; post-pneumothorax, tuberculous, or staphylococcal; and spontaneous tuberculous. Obviously, treatment must be individualized, but each group has characteristics that reflect prognosis and act as a guide to treatment, as seen in table 5. In the present series, post-resection tuberculous empyema was an acute reactivation of chronic drug-resistant disease in patients with advanced disease, and as such was hard to treat. In all cases the empyema was of the mixed infection type. Fistula was always present, and breakdown of the wound was frequent. Some of the patients died in the early stage of the disease. Those reaching a chronic phase were already beyond help of lesser procedures. Thoracoplasty was only palliative, and decortication, even with resection, was unlikely to succeed in the face of drug resistance, mixed infection, and poor general vitality. In the writers' experience, the best tolerated and most successful procedure has been the Schede type of thoracoplasty.

Post-resection staphylococcal empyema is always acute and, as such, usually responds well to treatment. The problem is one of the pleural-space sterilization plus obliteration, with the staphylococcal infection as yet not firmly entrenched. Lesser measures will often suffice. In the absence of fistula, aspiration plus chemotherapy may be all that is necessary for a satisfactory result. With fistula, catheter suction drainage may often end in cure. If the fistula fails to close and the space persists, thoracoplasty may be necessary. In active infections with temperature and purulent discharge, the operation should be done with the tube in place, and suction drainage should be continued for some time. In cases in which the

TABLE 5

GUIDE TO TREATMENT—44 EMPYEMAS

January 1, 1953–March 31, 1957

	Post-Resection		Post-Pneumothorax		Spontaneous
	Tuberculous	Staphylococcal	Tuberculous	Staphylococcal	Tuberculous
Characteristics	Acute with poor prognosis	Acute with good prognosis	Chronic with good prognosis	Chronic with uncertain prognosis	Variable
Treatment	*Fistula* Wound breakdown with open drainage. Schede	*No fistula* Aspiration *Fistula* Suction drainage thoracoplasty: tube no tube. Schede	*No fistula* Thoracoplasty Decortication *Fistula* Resection and decortication. Schede	*Fistula* Resection and decortication. Schede	Aspiration Decortication

infection has been rendered quiescent, the tube may be removed forty-eight hours before the thoracoplasty is done. Occasionally none of these measures are effective and one must resort to either resection plus decortication, or Schede thoracoplasty.

Tuberculous empyema complicating pneumothorax is a chronic condition with a relatively good prognosis. As pneumothorax is no longer in current use, empyema is usually long-standing in patients being treated, and in the writers' experience the patients have good general resistance and have drug-susceptible infections. Frequently, a mixed infection has not taken place. Because the condition is chronic, lesser measures, such as aspiration or catheter suction drainage, are not curative. When no fistula is present, thoracoplasty may be effective, but decortication gives better results, if tolerated, and at times it improves breathing capacity. Some writers, including Quinlan and associates (8), have reported good success from decortication in the presence of fistula. In the experience of the present writers, decortication plus resection have given better results. At times Schede thoracoplasty is the only procedure that can be tolerated.

Staphylococcal empyema complicating pneumothorax is a chronic condition with an uncertain prognosis. Unlike tuberculosis, chronicity in staphylococcal infection hinders rather than favors treatment even with good antimicrobial therapy. Major measures are necessary. Thoracoplasty may suffice, but chronic staphylococcal infection is difficult to eradicate and may recur even after a lapse of years, especially if fistula was originally present. Decortication plus resection may be necessary, and even this procedure may fail and the patient come to Schede thoracoplasty.

The spontaneously arising tuberculous empyemas have variable characteristics and usually reflect the presence of complicated underlying lung disease. In the presence of good general response to treatment, the spontaneous empyemas sometimes clear on aspiration and chemotherapy. In many the infection is solely tuberculous without secondary bacterial invaders. At other times major surgical procedures may seem indicated, but often the patient is too ill from his parenchymal disease to tolerate any active treatment of the empyema. In a few cases the empyema is primary, and decortication is effective treatment.

Details of treatment and results in the different forms of empyema are outlined in table 6 and require no elaboration. In table 7 may be seen the number of times when the various procedures were used as final treatment. Attention should be drawn in particular to two points. The first is the high mortality in open-wound drainage. This is to be expected as all patients had extensively diseased lungs, and 4 of the 7 in this category developed bronchopleural fistula after resection with extensive wound break-down from tuberculous infection. Second, one-fourth of all patients were treated with Schede thoracoplasty. It was used in both tuberculous and staphylococcal empyema when lesser measures had failed and resection and decortication were thought not applicable because of risk or technical considerations. In spite of these limitations, 5 patients so treated are well, 5 are still on treatment with reasonable chance of recovery, and only one is dead.

TABLE 6

DETAILS OF TREATMENT: 44 EMPYEMAS

January 1, 1953-March 31, 1957

	Well			Still Under Treatment			Dead			Totals	
		Number	Per Cent		Number	Per Cent		Number	Per Cent		
After resection, tuberculous	Wound break and open drainage—1 Schede—1	2	20	Schede—3	3	30	Wound break and open drainage—4 Thoracoplasty—1	5	50	10	
Staphylococcal	Aspiration—1 Suction drainage—4 Thoracoplasty—3 Schede—3	11	73.3	Schede—1	1	6.7	Aspiration—1 Suction drainage—1 Resection and decortication—1	3	20	15	25
After pneumothorax, tuberculous	Decortication—2 Resection and decortication—2 Schede—1	5	55.5	Aspiration—1 Schede—1	2	22.2	Wound break and open drainage—1 Schede—1	2	22.2	9	
Staphylococcal	Aspiration—1 Resection and decortication—1	2	50	Aspiration—1 Schede—1	2	50	—		0	4	13
Others, tuberculous	Aspiration—2 Decortication—1	3	50	Aspiration—2	2	33	Wound break and open drainage—1	1	17	6	6
		24	55		9	20		11	25		44

TABLE 7

RESULTS OF TREATMENT ACCORDING TO PROCEDURE

Procedure	Tuberculous			Staphylococcal			All Types			Total
	Well	Under Treatment	Dead	Well	Under Treatment	Dead	Well	Under Treatment	Dead	
Aspiration	2	3	0	2	1	1	4	4	1	9
Suction drainage	—	—	—	4	—	1	4	—	1	5
Thoracoplasty	—	—	1	3	—	—	3	—	1	4
Schede	2	4	1	3	1	—	5	5	1	11
Resection and decortication	2	—	—	2	—	1	4	—	1	5
Decortication	3	—	—	—	—	—	3	—	—	3
Open-wound drainage	1	—	6	—	—	—	1	—	6	7
Total	10	7	8	14	2	3	24	9	11	44
	40%	28%	32%	74%	10%	16%	55%	20%	25%	100%

The frequent use of Schede thoracoplasty in the present series deserves further comment. This operation is unpopular with both surgeon and patient due to the long postoperative period of open-wound dressings and the final scarring and at times deformity. It should be avoided whenever possible and, during the past few years, decortication, with or without resection, has taken its place in the successful treatment of many hitherto intractable empyemas. But resection and decortication cannot always be used, and certain conditions doom them to failure. Schede thoracoplasty may be applied to almost all such cases and often with success. Thus, in the present series, of the 11 patients treated with Schede operations, 4 had already had pneumonectomy, so further resection was not possible. All 4 had drug-resistant infections, and 2 had fistula. Three other patients had fistula with markedly reduced breathing capacity and poor general vitality which precluded resection. Of those cured by Schede, 2 were tuberculous and 3, staphylococcal. For successful management, it is believed that certain technical considerations are important. These involve first limiting the extent of the initial wound by suturing the skin well down into its depths; second, the repair of residual bronchocutaneous fistulas together with some plastic reconstruction of the chest wall. The details of such procedures are beyond the scope of the present paper.

Statistics on total results of the treatment of tuberculous empyema were not found in the literature. There seems no doubt, however, that the outlook is far from good when one considers all cases. The total results of treatment in the present series are shown in table 8: of the 44 patients, 24 are well, 9 are still under treatment, and 11 are dead. In the present series, in tuberculous empyema following resection: 2 are well, 2 are still being treated, and 3 are dead. When the cases of 3 very sick patients whose surgery was done elsewhere are included, the results are much worse: 2 are well, 3 are still under treatment, and 5 are dead. Prognosis is much better for staphylococcal empyema following

TABLE 8

RESULTS OF TREATMENT: 44 EMPYEMAS

January 1, 1953–March 31, 1957

Type	Well		Under Treatment		Dead		Totals	
	Number	Per Cent	Number	Per Cent	Number	Per Cent		
Post-resection, present series								
Tuberculous	2	28.5	2	28.5	3	43	7	
Staphylococcal	10	71.4	1	7.2	3	21.4	14	21
Post-resection, all cases								
Tuberculous	2	20	3	30	5	50	10	
Staphylococcal	11	73	1	7	3	20	15	25
Post-pneumothorax								
Tuberculous	5	55.5	2	22.2	2	22.2	9	
Staphylococcal	2	50	2	50	0	0	4	13
Others, tuberculous	3	50	2	33	1	17	6	6
	24	55	9	20	11	25	44	44

resection: of 14 such patients, 10 are well, one is still under treatment, and 3 are dead. In tuberculous empyema following pneumothorax: 5 are well, 2 are still under treatment, and 2 are dead. In staphylococcal empyema complicating pneumothorax: 2 are well, 2 are still under treatment, and none died. In spontaneous tuberculous empyema: 3 are well, 2 are still under treatment, and one died.

SUMMARY

The extent of the chronicity in pulmonary tuberculous lesions is basically responsible for post-resection empyema, both tuberculous and staphylococcal. Transection of diseased pulmonary tissue containing drug-resistant tubercle bacilli accounts for most tuberculous empyemas that develop after present-day surgery; active endobronchial disease at the site of bronchial resection is seldom a factor.

Tuberculous chronicity also sets the stage for staphylococcal empyema because of the inherent factors of respiratory sepsis, poor drainage, fibrosis with tissue devitalization, plus an increased potential for space problems due to impaired expansibility.

Tuberculous empyema complicating resection is uncommon since the use of long-term antimicrobial therapy. It is almost always present in patients with drug-resistant infections and is frequently intractable to treatment. The incidence of staphylococcal empyema following resection appears to be increasing. Fortunately it responds well to treatment and, although troublesome as a complication, seldom prevents recovery.

Pneumothorax, although no longer in current use, still accounts for a sizeable group of empyema patients. In the tuberculous variety, drug susceptibility is

usually still present, and response to treatment is good; but in the staphylococcal type of empyema, chronicity often makes the treatment difficult.

Although decortication, with or without resection, now is successful in many stubborn cases of empyema, there remains a residue of patients who respond only to Schede thoracoplasty.

Sumario

El Empiema como Complicación de la Tuberculosis Pulmonar

En la patología tuberculosa, la cronicidad es la causa fundamental del empiema, tanto tuberculoso como estafilocócico, consecutivo a la resección. La transsección de tejido parenquimatoso enfermo que contiene bacilos tuberculosos en enfermos farmacorresistentes explica la mayoría de los empiemas tuberculosos que se presentan después de la cirugía actual; la enfermedad endobronquial activa en el sitio de la resección endobronquial constituye rara vez un factor.

La cronicidad tuberculosa también prepara la escena para el empiema estafilocócico debido a los factores inherentes de sepsis respiratoria, mal drenaje, fibrosis con desvitalización de los tejidos, además de mayor potencialidad para crear problemas de espacio debidos a la afectada expansibilidad.

El empiema tuberculoso como complicación de la resección es raro desde el empleo de la terapéutica antimicrobiana a largo plazo. Obsérvase casi siempre en enfermos farmacorresistentes y es frecuentemente incoercible con el tratamiento. La incidencia del empiema estafilocócico consecutivo a la resección parece ir en aumento. Por fortuna, responde bien al tratamiento y, aunque molesto como complicación, raramente impide la curación.

El neumotórax, aunque no ya de empleo corriente, se usa todavía para un grupo considerable de enfermos de empiema. En la variedad tuberculosa, suele existir todavía susceptibilidad a las drogas y la respuesta al tratamiento es buena; pero en el empiema de forma estafilocócica, la cronicidad dificulta a menudo el tratamiento.

Aunque la decorticación, con o sin resección, cura hoy día muchos empiemas rebeldes, queda un residuo de enfermos que no responden más que a la toracoplastia de Schede.

Resume

Empyème compliquant la tuberculose pulmonaire

En pathologie tuberculeuse, la tuberculose est fondamentalement responsable de l'empyème tuberculeux ou staphylococcique qui peuvent succéder à l'exérèse pulmonaire. La section de tissus au niveau des lésions parenchymateuses contenant des bacilles tuberculeux, chez les malades résistant à la chimiothérapie, est responsable de la plupart des empyèmes tuberculeux qui se développent de nos jours après l'intervention chirurgicale; les lésions endobronchiques en activité au niveau de résections bronchiques sont rarement le facteur en cause.

La chronicité de la tuberculose prépare également le terrain pour l'empyème staphylococcique, car les facteurs inhérents à la septicité de l'appareil respiratoire, drainage insuffisant, sclérose avec dévitalisation des tissus plus un potentiel accru par les problèmes spatiaux erées par l'altération de l'expansibilité.

L'empyème tuberculeux comme complication de la résection est devenu rare depuis l'usage du traitement antibactérien prolongé. C'est presque toujours chez les malades résistant à la chimiothérapie qu'on l'observe et il est fréquemment réfractaire au traitement. Il semble que l'incidence de l'empyème staphylococcique succédant aux résections soit en progression. Heureusement, il répond au traitement de façon satisfaisante et cette complication, bien que gênante, prévient rarement la guérison.

Malgré l'utilisation restreinte actuelle du pneumothorax il est encore employé chez de nombreux malades affectés d'empyème. Dans l'empyème tuberculeux la sensibilité aux

antibactériens est habituellement encore présente et la réponse au traitement est généralement satisfaisante, mais dans l'empyème de type staphylococcique la chronicité rend souvent le traitement difficile.

Bien que la décortication, avec ou sans résection, guérit actuellement un grand nombre d'empyèmes tenaces, il y a encore un petit nombre de cas qui ne répondent qu'à la thoracoplastie de Schede.

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THE ARCANA OF TUBERCULOSIS

With a Brief Epidemiologic History of the Disease in the U. S. A. Part III.

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III. Epidemiologic History of Tuberculosis in the United States*

The Beginnings

Statements were made that tuberculosis must have been brought to the New World by the conquerors and missionaries. Quite to the contrary, there is ample evidence of pre-Columbian tuberculosis on the American continent.

Cases of lupus are depicted in Huacos pottery of old Peruvian origin (66); hunchbacks are not uncommon among Aztec figurines, such as those preserved in the Howard Dittrick Museum in Cleveland (67); and the old Mayo language (68) has three synonyms for consumptive (*nahbacil, yumulkabil, tzemil*), and a verb for wasting (*tzemtzem cimil*). Part of a vertebral column, badly damaged by caries, was found among prehistoric remains of North American Indians (specimen 17,223 in the Peabody Museum at Harvard); and clay figurines representing gibbous infants are occasionally discovered in Indian tombs.

Cases of what was believed to be consumption in early American Indians are found in many travelogues and other reports of the time.

In 1657, a full-blooded Huron girl was supposed to become a nun in a Catholic convent, but she died prematurely of a slow fever and cough, which wasted her lungs;[1] she could have contracted the disease during the initiation period, but the text specifies that her malady was not uncommon among the local tribes (69), and there are other instances of phthisis among the Indians reported by the Jesuits (70). Josselyn, who visited New England in the seventeenth century, lists consumption among the diseases encountered in Indians (71). French travelers of the eighteenth century found phthisis in American aborigines; for instance, La Hontan described it in Canadian Indians (72), Lafitau in the "*sauvages de la Nouvelle-France*" (73), and Rollin (surgeon of the ill-fated voyage of La Pérouse) in the "*indigènes*" of California (74).

Most writers seem to agree that there was no tuberculosis in the early American settlements, for instance in Virginia (75), but history has preserved infor-

* Parts I and II of this paper were published in the preceding issue of the Review.

[1] Even now, in the roentgenographic era, a positive diagnosis of tuberculosis requires histologic identification of specific lesions provoked by inoculation of suspected material into a laboratory animal. Any other findings are at best presumptive; therefore, historical (retrospective) diagnoses, based mostly on circumstantial evidence or hearsay, can be easily contested, as there are several etiologic possibilities to explain a slow wasting fever with cough or a gibbus. Nevertheless, the large majority of these "suspects" were most probably tuberculous. In a way of comparison, it may be wise to raise the question of paratubercle bacilli whenever a positive smear is the only evidence available, but experience has shown that, even today, in most such cases the organisms are *M. tuberculosis*.

mation regarding several persons who died of this disease in America prior to 1700. As it happens, all but one of them lived in New England.

Early sources (76) quoted by historians such as Bancroft (77), would indicate that many of the Mayflower expedition died of phthisis after establishing the Plymouth colony, especially in the dreadful winter of 1620. The earliest authenticated death attributed to phthisis in Massachusetts was that of its first clergyman, the frail Francis Higginson (1586–1630), who had come over from England on the Talbot in 1629 with a wife and eight children; he died in Naumkeag (Salem) one year later, after writing a diary which went through several editions. The pious scholar for whom the famous college was named, John Harvard (1607–1638), died of consumption, and so did *Père* Jacques Marquette (1637–1674), the Jesuit explorer of the Great Lakes. On American soil, the first recorded death of consumption in a physician was that of Leonard Hoar (1630–1675), a minister and doctor in "physick" from Cambridge (England), who in 1672 was elected to succeed Chauncey as the third president of Harvard. The pioneer printer and wood engraver, John Foster (1648–1681), a native of Dorchester, Massachusetts, and a Harvard graduate, lived with a "weak and languishing" body, and died of phthisis in the town of his birth.

At the beginning of the eighteenth century, tuberculosis was reaching epidemic proportions in the British Isles. In 1720, the physician and colonial administrator Cadwallader Colden (1688–1776) wrote about New York: ". . . we have few consumptions . . . People inclined to be consumptive in England, are often perfectly cured by our fine air, but if there be ulcers formed, they die in a little time" (78). John Tennent, who "discovered" the snake-root (*Polygala senega*), recommended it for "Consumptions of several kinds" and "Hectick Fevers," which by his statement were not uncommon in Virginia in the first half of the eighteenth century (79). These testimonials are corroborated by a slight increase in the incidence of "historical consumptives" in that period.

Cotton Mather's wife died of consumption in Boston in 1702, and Mather's nephew, Thomas Walter (1696–1725), a clergyman remembered for having dared to cooperate in smallpox vaccinations, succumbed to phthisis. Andrew Hamilton, a former Scottish merchant, who came to America in 1686 and became the deputy governor of Pennsylvania, and later the last proprietary governor of the East and West New Jerseys, died of "hectic fever" in 1703. A touching story (80) details the consumptive death of the mystic Johann Kelpius (1673–1708), who had arrived from East European Transylvania to preach his peculiar orthodoxy (overlain in true rococo fashion with cabalism, chiliasm, pietism, and Rosicrucianism) to the settlers who built Germantown in the primeval forests of Pennsylvania. Phthisis killed the puritan female poet Jane Turell (1708–1735) and the devoted, though highly emotional, missionary to the Indians, David Brainerd (1718–1747). The American-born portraitist and "mariner" Robert Feke (1705–1750), of English stock and affinity, attempted to escape his fate by going to the Barbados, but it became his last journey.

In North America, the first significant rise in the incidence of consumption occurred in the second half of the eighteenth century. In his chapter on "catarrhal consumption" (80a), Lionel Chalmers (1715?–1777) wrote: "This may be properly called the consumption of *Carolina*; for that sort which happens from a *vomica*, or an *aposthemation* is more rare with us: whereas *catarrhal phthisis* is

frequent and proves equally mortal with the other . . ." The French nobleman De Warville reports that after the American Revolution consumption became the most frequent cause of death in Philadelphia, perhaps even in Pennsylvania (81); he mentions that, following the war, it had increased also in other states, for instance in Virginia. In fact, a stormy upsurge occurred at that time in the number of phthisics in all walks of life, but especially among the wealthy and the dignitaries.

Tuberculosis was not uncommon in the family of George Washington (1732–1799), who in 1751 accompanied his phthisical half-brother Lawrence Washington (?–1752) on a trip to the Barbados. As a matter of fact, G. W. P. Custis, in describing his adoptive father, George Washington (who died of *cynanche trachealis*), stated that "his chest, though broad and expansive, was not prominent but rather hollowed in the center. He had suffered from a pulmonary infection in early life from which he never entirely recovered."

The Boston patriot of tea-party fame, Josiah Quincy, Jr. (1744–1775), died of consumption on his return trip from London. The list also contains two Revolutionary soldiers, George Baylor (1752–1784), born in the Shenandoah Valley of Virginia, bayoneted through the lung (post-traumatic tuberculosis ?) by one of the men of "No Flint Grey" and deceased at Bridgetown, Barbados, and Otho Holland Williams (1749–1794), who made his trip to the Barbados in 1793. The lawyer, teacher, philosopher, and revolutionary leader, William Churchill Houston (1746–1788), deputy secretary of the Continental Congress, never reached the sunny South because he died on the way, in Frankford, Pennsylvania.

Ministers of all faiths paid a heavy tribute to phthisis: J. C. F. Cammerhoff (1721–1751), the Moravian missionary, who joined the Oneida Indians under the name of Gallichwio (Good Message) and was the last "Wetteravian" in this country; Nathaniel Evans (1742–1767), a native of Philadelphia, clergyman of the Church of England and one of the first American poets ("And this new world ne'er feel the muse's fire,/ No beauties charm us, or no deeds inspire?"); J. R. Hardenbergh (1736–1790), a reformed clergyman of Dutch ancestry, who became the first president of Queen's (Rutgers) College, and died after four years in office; the "most amiable ex-Jesuit" and catholic missionary, Lawrence Graessl (1753–1793); and the disrupted Baptist, Elhanan Winchester (1751–1797), who professed the doctrine of Universal Restoration.

Thomas Greenleaf (1755–1798), the colorful and controversial New York printer and journalist (as a staunch American individualist, he did not spare even the "venerable Washington" from a "great degree of virulence") was weakened by a "slow wasting consumption," but is said to have died of yellow fever. There is no doubt about the etiology of the final hemoptoic episode in the short life of the conservative (anti-Jacobin) Philadelphia poet, William Cliffton (1772–1799). He was of old Quaker stock, which is in line with the statement of Currie, who wrote in 1792: ". . . the greatest proportion of those who die of this malady (in Philadelphia) belong to the society of Friends."

A most representative figure of wealth and beauty in her time was the wife of William Bingham (he founded Binghamton, New York, and the first chartered bank in this country), "Queen" Anne Willing Bingham (1764–1801) of the "Republican Court" at "Mansion House" in Philadelphia, where George Washington often visited as a friend of the family; shortly after the birth of her only son, "Queen" Anne had an attack of lung fever, which rapidly grew so serious that a milder climate was advised; whereupon she was taken on a yacht to Bermuda, but died after a few months.

There occurred also an increase in the number of consumptives among well-known

physicians. The famous New Haven case histories (82)—which include a broncholithiasis associated with fatal phthisis—contain the princeps description of congenital pyloric stenosis ("schirrhus in the pylorus of an infant") by Hezekiah Beardsley (1748–1790), and one of the first American observations of tuberculous meningitis ("hydrocephalus internus") by Ebenezer Beardsley (1746–1791); the Beardsleys were brothers, and both died of *tabes pulmonalis*. Alexander Garden (1728–1791), for whom is named the Cape Jessamine (*Gardenia jasminoides*), was a Scottish physician who lived for thirty years in South Carolina (1752–1782). He refused a professorship in the New York Medical College because of the same disease which, after several bouts, was going to kill him in London. Nathaniel Walker Appleton (1755–1795) was first apprentice to the centenarian Holyoke; then he graduated from Harvard, and finally became the first secretary of the Massachusetts Medical Society. He was a life-long consumptive, and in 1794 moved to Marietta, Ohio, but his health was not much benefited by the Western excursion (in those times the consumptives who could afford it went to the Caribbean; the others just went West), and he returned to die in Boston. A special mention is deserved by Lemuel Hopkins (1750–1801), born in Salem (his mother and her family were consumptive), who was a rival of Rush and one of the earliest American phthisiologists. During his last illness, notwithstanding the opposition of friends, he was repeatedly bled for hemoptyses, but lived to resume his practice, only to die soon afterwards.

The venerated Edward Augustus Holyoke (1728–1829) was renowned for many unusual feats, for instance the cure of one of his daughters (who had become consumptive), by using prussic (hydrocyanic) acid[2] (84). He kept meteorologic records, and was a respected member of the American Academy of Arts and Sciences; in their *Memoirs* he published one of the earliest mortality statistics in this country (85). This was for the years 1782 and 1783. He was also the author of a memorable continuation, entitled "Observations on the Weather and Diseases at Salem," read before the Massachusetts Medical Society in 1786. By averaging the data for these three years, with reference to the population of Salem (estimated at 9,000), one arrives at the rate of 300 deaths due to consumption per 100,000 population. But perhaps even more important than this first tuberculosis death rate for a town in North America is the statement made by Holyoke: "I shall conclude with observing, what I suppose must have been observed by all the elder Practitioners among us, that acute diseases are much less frequent among us in this town, as well as much less fatal than formerly; and that Chronic diseases, particularly Phthisis Pulmonalis, have taken their place."

The "elder practitioners" were excellent observers, and their appraisal was impeccable: in the newly born, and desperately struggling United States, tuberculosis had become, as in John Bunyan's England of 1680, the "captain of all the men of death."

The First North American Climax

Bills of mortality had been published irregularly in a few American cities even prior to 1750; for instance, those found by Pehr Kalm during his visit to Philadelphia. After 1800, several municipalities began to tabulate regularly the number of deaths by causes (86).

[2] Those interested in reviving this form of therapy are referred to the prescriptions offered by Green (83).

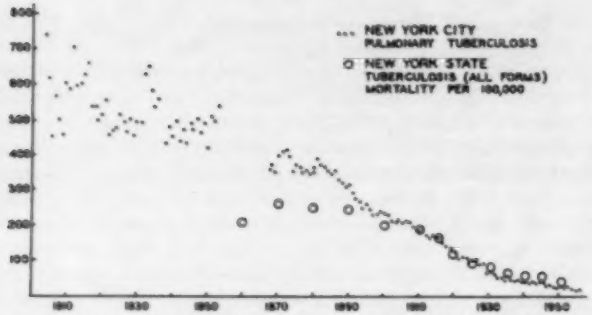

FIG. 8. The peak of the New York City curve occurred before 1800, i.e., prior to the beginning of registration of deaths by causes. Erratic variations of the death rate in the first decades may be due to inadequate registration. The "Irish" peak is barely seen because figures are missing for this period. Early (after 1870) and late (after 1880) "Negro" peaks are definitely identifiable. New York State data would suggest a climax around 1870, which must be regarded as an average because its territory contains a very heterogenous population, with wide variations between "downstate" and "upstate" circumstances. The typical deceleration of the exponential tracing is well demonstrated. *Source:* New York City Department of Health and New York State Department of Health (*see also* footnote 3).

Significant series were accumulated, such as the sesquicentennial New York City tracing[3] (figure 8). Even state-wide mortality data were printed, and among these Massachusetts has the longest run[4] (figure 9), because in 1842 appropriate legislation was enacted upon the insistence of the far-sighted lawyer, genealogist, and statistician, Lemuel Shattuck (1793–1859). This promoted the interest in vital statistics, and, with Shattuck as expert adviser, it resulted in the first nation-wide attempt to obtain mortality data in conjunction with the seventh United States census in 1850 (87). A similar, decennial sampling of more and more detailed figures (88) was continued to the twelfth census. In 1880, federal initiative created the death registration area, which consisted initially of three members (District of Columbia, Massachusetts, and New Jersey). States and cities were included as soon as their registration was demonstrated to be at least 90 per cent complete. Beginning with 1900, the Bureau of the Census issued yearly mortality reports, based on mortality returns from the registration area, which in 1900 included ten states (Connecticut, Vermont, Indiana, Maine, Massachusetts, Michigan, New Hampshire, New Jersey, New York, Rhode Island), and the District of Columbia. In time, all of the states joined the area, the last one being Texas in 1933. Since 1945, the death rates are published together with other data compiled by the National Office of Vital Statistics (89).

It would seem that only figures collected in the last twenty years provide adequate geographic coverage as well as reasonable comparableness. This is correct when actuarial accuracy is desired. The incompleteness and unreliability of statistics in general, and of older figures of varied provenience in particular, may be disregarded for the purposes of

[3] The *city* figures were obtained through the graciousness of Miss Frieda Greenstein, Senior Statistician, City of New York Department of Health, while *state* figures after 1900 were contributed by Mrs. Mary E. Thompson, Senior Biostatistician, State Department of Health, Albany.

[4] This series was provided by Mr. Arthur J. Hasset, State Registrar of Vital Statistics of the Commonwealth of Massachusetts.

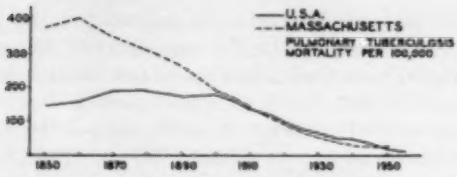

FIG. 9. Both the United States and the Massachusetts curves were inscribed from decennial points prior to 1900; thereafter from quinquennial data. It is interesting to compare this appearance with the theoretical crossings in figure 3. The comparatively higher urbanization of the Old Bay State resulted in the faster decrease, but another crossing occurred shortly before 1950, presumably due to the increase in the general level of urbanization in the United States and to the proportionally larger foreign-born population in Massachusetts. *Source:* National Office of Vital Statistics and State Registry of Vital Statistics of the Commonwealth of Massachusetts (*see also* footnote 4).

an historic study, in which the data are used solely for the identification of local, regional, and national trends.[5]

The achievement of independence by the United States coincided with (or may have been causally related to) a steep increase in the number of its popula-

[5] A lengthy correspondence was exchanged with many statistical offices around the country. Some of the contributions are acknowledged in connection with the specific utilization of the respective figures. Many others had to be edited from the final version, since they would not give additional information or because they were incomplete. Credit is given here to the following persons: in Alabama, Dr. O. L. Chason, City-County Board of Health Officer in Mobile; in California, Miss Joanna Sheng, Statistician of the City Department of Public Health in Oakland, and Miss Mae Goshert, Chief, Bureau of Records and Statistics of the City-County Department of Public Health in San Diego; in Connecticut, Miss Lillian Konick, Statistician of the City Department of Health in New Haven; in Illinois, Mr. John H. Vinyard, Statistician of the State Department of Public Health in Springfield; in Minnesota, Miss Jean Roberts, Director of the City Bureau of Public Health, Records, and Statistics in Minneapolis; in Missouri, Mr. Clyde A. Bridger, Director, State Bureau of Vital Statistics in Jefferson City, and Miss Bessie W. Smith, from the City Communicable Disease Division, and Miss Neva Minshall, from the City Bureau of Vital Statistics, both in Kansas City; in New Mexico, Dr. J. T. Marshall, Director, Division of Chronic Diseases of the State Department of Public Health in Santa Fe; in New York, Dr. Rachel M. Jenss, Director of the Office of Biostatistics of the Erie County Health Department in Buffalo, and Mr. Robert V. Frei, Statistician of the County Department of Health in Rensselaer; in Ohio, Dr. Carl W. Wilzbach, Commissioner of Health in Cincinnati, and Mr. Charles E. Zimmer, Statistician, City Division of Health in Dayton; in Oklahoma, Dr. J. Paul Haney, from the City-County Health Department in Tulsa; in Oregon, Dr. Thomas L. Meador, City Health Officer, and Miss Deane Huxtable, State Board of Health Registrar, both in Portland; in Pennsylvania, Dr. F. Herbert Colwell, Director, Office of Statistics and Research of the Department of Public Health in Philadelphia, and Mr. Joseph Miller, Chief Statistical Clerk in the City Department of Public Health in Pittsburgh; in Texas, Mr. E. E. Bryant, Registrar of Vital Statistics in Dallas, and Mr. W. H. Alban, Director of Administration and Records in Houston; and in Washington, Miss Marques Miller, Statistician of the State Department of Health in Olympia. Although some of them viewed the requests for data with suspicion, as a rule the figures were as accurate as they had been registered in the respective offices. Also, it must be emphasized that, without the active help of all concerned, this publication would not have been possible.

tion, both by birth and immigration. The growth and the beginning industrialization were most visible in the Eastern seaports, where the reinforcing effect of war produced a marked *urbanization* (*see* definition of term in Part II). This resulted in the first North American peak of tuberculosis mortality, which occurred around 1800 in the metropolitan areas of the Atlantic seaboard. The highest death rate must have exceeded 1,000 and might have been as high as 1,500 per 100,000 population. The first mortality statistics appeared at about the same time, and they were viewed with grave concern. For instance, Sam Mitchill (1764–1831) wrote in 1808: "The extensive prevalence of consumption is a subject of the most serious consideration. The deaths under that head amount to about one fifth of the whole" (90). Most observers explained this epidemic of phthisis "throughout the whole Eastern coast of the United States" as being "induced by the vicinity of the sea, the prevalence of North-East winds, and sudden changes in air temperature" (63).

A similar spiking occurred in the incidence of "historical" consumptives. Among the tuberculous figures in New York were the surgeon Valentine Seaman (1770–1817), who introduced smallpox vaccination; the physician, druggist, and poet Joseph Rodman Drake (1795–1820), who wrote "The Culprit Fay" and "The American Flag"; the Lutheran clergyman Friedrich Christian Schaeffer (1792–1831), remembered for having resisted union with the Episcopalians; the Talmudist and Hebrew grammarian Isaac Nordheimer (1809–1842), sole Jewish faculty member of the all-Presbyterian Union Theological Seminary; the brothers and painters, Frederick St. Agate (1803–1844) who was one of the initiators of the National Academy of Design, and Alfred T. Agate (1812–1846), who participated in Wilkes Antarctic expedition; David Abeel (1804–1846), too frail to be accepted at West Point or to study medicine, but whose will was strong enough to make him an ardent missionary; and the physician John Wright (1811–1846), professor of natural history at Rensselaer and intimate friend of Audubon.

At that time, the capital city of the newborn nation was Philadelphia. In a contemporary diary, "one finds frequent mention of consumption as causing the death of friends and acquaintances" (90*a*). First on the list of famous consumptives in the Quaker state is the brilliant physician John Richardson Young (1782–1804), who graduated in 1803 from the University of Pennsylvania with an experimental thesis on the digestive process, including the then new finding that acid was secreted by the stomach; Young's mother and sisters died also of tuberculosis; Charles Brockden Brown (1771–1810) who was the first American novelist to achieve international reputation; Michael Egan (1761–1814), who became the first Catholic bishop of Philadelphia; the pharmacologist, physician, and naturalist, Benjamin Smith Barton (1766–1815), successor of Rush in 1813 in the chair of Theory and Practice of Medicine, who published the first U. S. *Materia Medica*; and the physician and Lancastrian and Pestalozzian enthusiast, John Miller Keagy (1792–1837), professor of Natural Sciences at Dickinson College.

The list may be continued for neighboring southeastern states: in New Jersey, the professor of Anatomy at Rutgers and co-editor of the *American Journal of Medical Sciences*, John Davidson Godman (1794–1830), author of an *American Natural History* in three volumes (1826), whom "poverty pursued from the cradle to the grave"; in Maryland, the poet, naval surgeon, and diplomat, John Shaw (1778–1809), who in 1805 founded the College of Medicine in Baltimore; and the abolitionist clergyman, Charles Turner Torrey (1813–1846), who became psychotic and died consumptive in prison after being

sentenced to hard labor for having freed somebody else's slaves; in Virginia, the delicate, Irish-born physician, John Patten Emmett (1796–1842), professor of natural history, and later of materia medica, in the University of Virginia; in North Carolina, the physician Moses John DeRosset, II (1796–1826); and in Georgia, the miniature painter Edward Greene Malbone (1777–1807), who died there while on a return trip from Jamaica to Rhode Island.

In 1815, the physician Joseph Adams Gallup (1768–1849) published *Sketches of Epidemic Diseases in the State of Vermont*, to which he added *Remarks on Pulmonary Consumption*, because of an "evident constitutional propensity to the disease in himself, and the loss of several of his nearest connexions by it," perhaps due to the fact that "empyricks, quacks, impostors, mountebanks, horse-doctors, and patentees, have imposed, upon credulous and suffering patients, their never-failing tinctures, essences, sirups, balsams, lozenges, anodynes, pulmonic detergents, nostrums, and catholicons." Gallup, who did not believe that phthisis ("scourge of physicians") is contagious, reported its numerical increase in northern New England at that particular time (91).

The enumeration of famous Yankee consumptives starts with the theologian and educator Jesse Appleton (1772–1819), who died during his tenure as president of Bowdoin College; Francis Brown (1784–1820), who had been college president at Dartmouth, but did not die in office (he tried unsuccessfully to make a southern trip); the physician John Doane Wells (1799–1830) who was professor of anatomy and surgery both at Brunswick and at Berkshire; the anatomist Benjamin Lincoln (1802–1835), who devised an astonishingly modern (but never-tried) plan to reorganize medical education in Vermont; the poet Grenville Mellen (1799–1841), remembered for the Bunker Hill ode ("and high above the fight the lonely bugle grieves"); and the Puritan poet in the Miltonic tradition, Sumner Lincoln Fairfield (1803–1844), who published *The Last Days of Pompeii* in 1832, two years ahead of his plagiarist, Bulwer.

The Massachusetts list begins with Peter Thacher (1752–1802), a Congregational clergyman who died in Havana, and his son, Samuel Cooper Thacher (1785–1818), theologian and librarian at Harvard, who made numerous sea voyages in his last years of life, and died in France; it continues with the sea captain, merchant, Jeffersonian sympathizer, and Salem congressman, Jacob Crowninshield (1770–1808), who had a hemoptysis while finishing his last speech in the House of Representatives; the blind Levi Frisbie (1783–1822), who became Latin tutor and teacher of natural religion, moral philosophy, and civil polity at Harvard; John Lowell (1799–1836), who founded in Boston the institute which bears his name and, after consumption killed his wife (1830) and two daughters (1831), went to Bombay to die of the same disease; the mathematical prodigy and Methodist minister, Zerah Colburn (1804–1839), who became professor of language in Norwich University; the prolific author of *Indian Biography*, Benjamin Bussey Thatcher (1809–1840), who backed the Liberian experiment of the American Colonization Society; and the poetess Frances Sargent Osgood (1811–1850), who, although married since 1835 (to a painter), became "closely associated" with Edgar Allan Poe in 1845–1847, a friendship which led to Poe's libel suit against Thomas Dunn English.

Even though the first urban tuberculosis climax in America was over, consumption remained at the "head of all others (illnesses) in fatality" (92). And yet, Shattuck, who was still calling phthisis "the leading disease of this class,

and indeed, of all classes" (86), recognized that in 1840 it was already on the decrease.

At the height of the tuberculosis peak, the lethality had been terrifying. For instance, the physician, linguist, and Irish rebel, William James Macneven (1763–1841), who married in 1810 the daughter of a Long Island magnate, lost most of his children in early life due to tuberculosis. As time went on, instances of recovery were being recorded, such as the case of the Delaware physician Henry Latimer (1752–1819), who served as the surgeon of a "flying" hospital in the War of the Revolution; Rush speaks of him, and mentions his frequent hemoptyses and cough. Later, Latimer returned to private practice, his health improved. He then turned to politics, was appointed United States Senator (1795–1801), and became Surgeon-General of the Army (1813–1815). Actually, Rush "cured" many of his consumptive patients, some of them by horseback riding, as seemed to have been the case with William Drinker (1767–1821) of Philadelphia (90a). Well substantiated is the observation of the celebrated mathematician and navigator Nathaniel Bowditch (1773–1838), who became sick in 1808 (cough, hemoptyses, loss of weight), and cured himself by taking an open buggy ride of several weeks through the New England countryside; this story was related to the American Climatological Association in Boston in 1889 by the former patient's son, the famous chest specialist Henry Ingersoll Bowditch (1808–1892), who concluded by giving the autopsy findings at his father's death from carcinoma of the stomach, at which time the pulmonary scar was also identified. In this category belong also the colorful quack, Constantine Samuel Rafinesque-Schmaltz (1783–1840), inventor of the *Pulmel* (93), as well as the agricultural editor and writer, Willis Gaylord (1792–1844), crippled by Pott's disease at the age of twelve years.

The founder of Harvard Medical School, John Warren (1753–1815), of tea-party fame, and later president of the Massachusetts Medical Society, acquiesced in 1805 that consumption "is much more prevalent of late years than formerly," but specified that "in the populous seaport towns, the mortality from this disease is considerably greater than in the country" (94). In the absence of figures, it is difficult, if not impossible, to determine, with any degree of certainty, the dates at which the comparatively shallow (essential) peaks of tuberculosis mortality occurred in the original Atlantic seaboard states. If the European interval of fifty years between capital and country is valid, these Eastern rural peaks were surmounted not too long after the middle of the nineteenth century. Meanwhile, together with the pioneers, tuberculosis had started to spread along several Western trails.

Tuberculosis and the Frontier

In most instances, the West was conquered after a set pattern. Missionaries, hunters, and Indian traders would open new routes, along which came the ranchers. The cattle domains, with their floating cowboy population, would then be infiltrated by farmers, first in isolated settlements, later (after the sometimes inevitable "ranch war" for water supply) united in established communities, a few of which would become commercial and/or industrial centers. In this scheme, tuberculosis was present from the very beginning (there were many consumptives among the missionaries), but the curves preserved their "rural" shape for a long time. Even toward the end of the nineteenth century there were states in the Midwest which had not reached the degree of urbanization required for a

significant spiking of tuberculosis mortality. These states surpassed this degree of urbanization in the twentieth century, but at that time the level of immunity was so high as to preclude significant deflections of the tuberculosis death rate (figure 10).

Soon after solid "beachheads" had been established on the Atlantic coast, the early colonists were tempted to penetrate the "hinterland." The British attempted to restrain any expansion by promulgating in 1763 the old Proclamation Line, but this was disregarded almost from the beginning, and in 1775 Daniel Boone founded Boonsboro in Kentucky. The Westward movement never proceeded as an unbroken front, but followed certain routes. Further to the North there was an easier way, where no mountains intervened, into western New York, northern Pennsylvania, and Ohio. Moreover, the passage of the Northwestern Ordinance by Congress in 1787 channeled a steady flow of settlers into Ohio, which became a state in 1803, followed by Indiana in 1816, and by Illinois in 1818.

There must have been many tuberculous settlers, recruited as they were among the younger age groups of a heavily tuberculized population. New England furnished most of the pioneers for the Ohio Valley; and in 1809 Amherst, Massachusetts, had for its 1,600 inhabitants five deaths due to consumption (95), which corresponds to more than 300 per 100,000 population. At about the same time (thirty years after the first settlement), phthisis pulmonalis was fairly common in Wheeling, according to the account of a witness (96), though this may have been somewhat exaggerated. Fifty miles further to the south, and on the other side of the Ohio River, was Marietta. Of this town we have a detailed description, given by the reliable Samuel Prescott Hildreth (1783–1863), who specified that very few cases of phthisis occurred until the year 1808, and these did not average more than one death a year in a population of 2,000; since the year 1815, consumption had been gradually increasing, and in 1830 the annual average reached two deaths in one thousand inhabitants (97), which is 200 per 100,000 population.

Among early consumptives in the West was the Massachusetts lawyer, journalist, and author, David Everett (1770–1813), who lived the last eight months of his life in Marietta, Ohio. Israel Pickens (1780–1827), who was from North Carolina, became the third governor of Alabama, the first ex-officio president of the University of Alabama, and was even appointed to the United States Senate, but had to withdraw, and went to die in Cuba. British-born Robert Best (1790–1830) worked as a curator and artist of the Western Museum in Cincinnati, went as a lecturer in chemistry to Transylvania Univer-

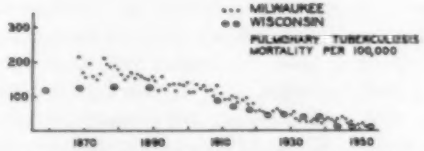

FIG. 10. The Milwaukee tracing is the most "rural" of the cities herein presented, but even more rural are the curves of Omaha, Iowa City, Kansas City, Minneapolis, and Salt Lake City. The (obviously "German") Milwaukee peak occurred in the 1860s, the Wisconsin climax, in the 1880s. *Source:* Milwaukee City Health Department and National Office of Vital Statistics.

sity, graduated as a physician in 1826, but died four years later of consumption. The first distinctively American sculptor, the Ohio-born Shobal Vail Clevenger (1812–1843), made busts of many people; yet his last work, the nude, life-sized figure of an Indian warrior, was never found. Tennessee-born John Murrell (1804–1847), a famous desperado, committed highway robberies from Georgia to New Orleans, and even planned a Negro uprising, but died of consumption in prison after being convicted of Negro-stealing. The Boston zoologist, Amos Binney (1803–1847), took a long horseback ride to Cincinnati in the hope it might improve his pulmonary illness, but this improvement was of short duration. The New Hampshire physician, Noah Worcester (1812–1847), went to Ohio and published one of the earliest texts on dermatology (Philadelphia, 1845); he married his childhood sweetheart, the Vermont-born Jane Shedd, and they both died of tuberculosis (she in 1843, after one year of marriage). The New Hampshire-born and New York-educated John Stoddard Butterfield (1817–1849) became professor of medicine in Willoughby University of Ohio, later was a co-founder and dean of Columbus Medical College, and founder of the *Ohio Medical and Surgical Journal*. When he was overcome by generalized tuberculosis, he returned to die in Salisbury, New Hampshire. The last on this list is Thomas Ford (1800–1850), who came from Pennsylvania to become Democratic governor of Illinois (1842–1846) and historian of its beginnings. He was later accused of playing the Mormon vote, fell into disgrace, and lost everything; he was dependent on charity at the time of his death from consumption.

At the beginning of the nineteenth century, California was under Spanish rule and, therefore, subject to the phthisiophobia which prevailed at that epoch in Latin-European countries. In following the ordinance of Ferdinand VI (98), Juan de Dios Morelos, chief surgeon of California (1800–1802), ordered the incineration of the belongings of several persons who had died of phthisis. During the governorship of Pablo Vicente de Sola, Count Hermenegildo Sal died of phthisis at Monterey. The late count had willed his clothing and furniture to charity, but they were burned anyway, and in the process the money and jewelry were lost or stolen and had to be replaced by the authorities (99). In 1804 an epidemic occurred among the Indians, which resulted in a sanitary evaluation of the missions. The report issued after the investigation lists consumption among the existing diseases.

These, however, were isolated instances. During the first half of the nineteenth century, tuberculosis was rarely encountered in the southwestern sections of North America. Joseph E. Field, who had escaped the Goliad massacre, attests to the scarcity of consumption in Texas in the 1830s (100), and this was corroborated in the 1840s by another physician, William Kennedy. Even in 1863 consumption was not mentioned in a study of the epidemic diseases of the area (101). In New Mexico, it was only after 1880 that the influx of "health-seekers" began to give some consistency to the tuberculosis figures (102). In California, as late as 1850, a person coughing in church would attract attention, except around San Francisco where tuberculosis was already on the upswing. Conversely, San Diego was so free of phthisis (103) that in 1853 Lieutenant Lewis Cass Hunt (1824–1886) of the U. S. Army was sent to Southern California because of a recently developed consumption (104). Hunt recovered, and in 1859 achieved fame as a captain when he occupied, on orders from General

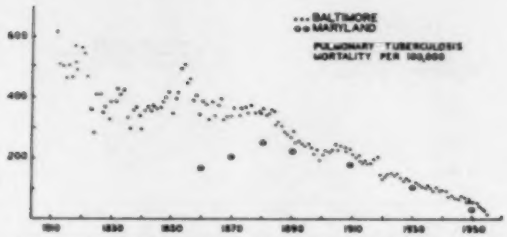

FIG. 11. After the erratic variations in the first decades of registration, the outstanding "Irish" peak after 1850 appears. Strangely enough, the Civil War peak cannot be identified. The "Negro" peak in the 1880s is more pronounced in the Maryland State curve. *Source:* Baltimore City Health Department (*see* footnote 6) and National Office of Vital Statistics.

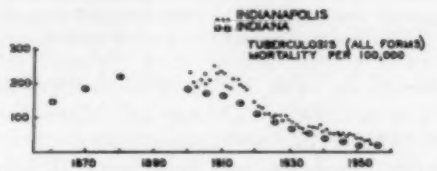

FIG. 12. The Indiana state curve reached its peak in the decade prior to that of Wisconsin state. No Indianapolis figures are available before 1900, with the exception of very fragmentary data, too unreliable for comparison. *Source:* Indiana State Board of Health (*see* footnote 7) and National Office of Vital Statistics.

("Old Fuss and Feathers") Winfield Scott, the San Juan Islands in Puget Sound during the boundary dispute with the British.

In the meantime, the settlers in the Western Plains were comfortably transcending a very shallow, almost imperceptible tuberculosis mortality peak.

The Midwestern Climax

As a convenience in presentation, the date of the first tuberculosis climax in North America was given as 1800, which is an average. The first peak occurred in all likelihood in the temporary capital of the newborn Union, Philadelphia, in the 1780s or 1790s. Baltimore and New York had their peaks shortly before 1800, and other Eastern ports (New Haven, Providence, Boston) followed at brief intervals. Their curves resemble that of Baltimore[6] (figure 11). Successive peaks marked the counterclockwise trail of the pioneers leading toward the Ohio Valley. In this area, the earliest available tuberculosis death rates are dated 1855 in Buffalo, 1875 in Pittsburgh, 1856 in Wheeling (105), and 1870 in Cincinnati. Chicago has figures going back to the 1850s; St. Louis and Milwaukee, to the 1860s; and Omaha, to the 1870s. None of the peaks went beyond 500 (most of them were below 300) per 100,000 population. The actual climax

[6] This long run, in part taken from Howard (1), was completed through the courtesy of Mr. Todd M. Frazier, Director, Bureau of Biostatistics of the City Health Department in Baltimore.

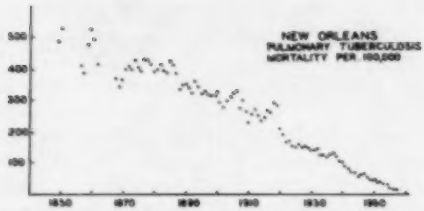

FIG. 13. The "first" peak must have been surmounted prior to 1820, long before the start of regular registration of deaths by causes. Prior to, and during, the Civil War, data are too fragmentary for evaluation, but the "hill" in the area of the "Negro" peak can be identified. The deflection after 1900 may be related to the Spanish-American War, or to the influx of Central American immigrants after that war. The World War I "hump" is seen, but in World War II little change occurred in New Orleans tuberculosis death rates. A small but noticeable deflection is seen in the 1930s (compare with the Charleston tracing in figure 17). *Source:* Public Health Training Center in New Orleans (*see* footnote 8).

may have taken place in the 1830s in Cincinnati; in the 1840s in Indianapolis[7] (*see* also figure 12); in the 1850s in Chicago and Milwaukee; in the 1860s in Omaha (106); in the 1880s in Salt Lake City, et cetera.

However inadequate (incomplete and inaccurate), the decennial statistical mortality reports issued by the Bureau of the Census (87, 107) received considerable attention. They provided a cross-section of the situation at a given date, and seemed to prove that there was a high mortality from consumption in every state and territory north of the thirty-eighth parallel (108), there apparently being a gradual decrease in tuberculosis mortality from North to South and from East to West (109). These facts were explained as being related to climate, although we realize today that they were only phase aspects in the development of the American cycle.

As early as 1853, an editorial in a southern medical journal stated: "It has become a popular error to suppose that consumption is developed almost exclusively in Northern latitudes. Look at our weekly bills of mortality! Are not nearly one-fifth of these put down as caused by phthisis pulmonalis? Most of whom are old residents of the city or natives of the place" (110). This is corroborated by the figures analyzed in the *Diseases of the Interior Valley* (111) in which Daniel Drake (1789?–1852) contends that in the late 1840s the death rate from consumption was 490 in New Orleans[8] (figure 13) and 370 in Charleston. The first peaks in the southern cities must have occurred not too long after those of the Eastern seaboard, probably in the 1820s and 1830s. In the old South, the discrepancy in *urbanization* between the larger cities and the surrounding territories was more pronounced than in any other section of the United States, and this may account for the alleged rarity of tuberculosis below the Mason-Dixon line prior to 1850.

[7] Most of the Indiana figures have been graciously contributed by Mr. Robert A. Calhoun, Director of Statistical Research of the Indiana State Board of Health.

[8] This long series was provided entirely from the records of Dr. Ben Freedman, Director of the Public Health Training Center in New Orleans.

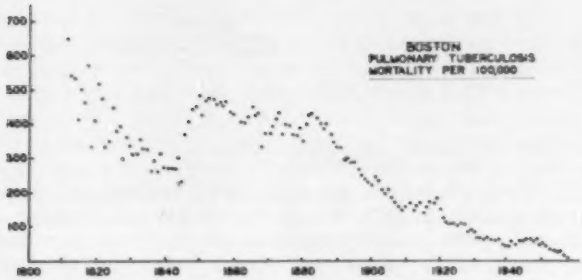

FIG. 14. The first or essential climax must have occurred just short of the beginning of regular registration. Very pronounced is the "Irish" peak in the 1850s, continued with a noticeable Civil War deflection, then with the early (1870) "Negro" peak, and another accident in the 1880s (probably a composite) including overlay of Southern and Eastern European immigration. In fact, because of the constantly high percentage of recent immigrants present in the "Hub," the World War I and II accidents are quite visible. *Source:* Boston Health Department (*see* footnote 9).

The original colonizing groups which reached the Eastern shores of North America were mainly of English stock (with minor Dutch, French, and other European components). Substantial immigration started only after 1820; yet by 1860 there were more than four million foreign-born living in the United States. Of those who arrived between 1850 and 1860, nearly one million were German, another million Irish. Most of the Irish were poor (they had left their country after the famine of 1846), wanted *jobs*, and therefore preferred the East. They caused a very noticeable peak on some tracings, for instance in Boston[9] (figure 14). The Germans, expatriated because of political disturbances (1848), were seeking *homes*, and found them by settling in the Midwest. This corresponds to a visible deflection on the Chicago[10] curve (figure 15).

Among famous consumptives in the North prior to the Civil War were the physician William Power (1813–1852), who taught Laënnec's auscultation in Baltimore (Maryland stayed with the Union, thus it may be considered as belonging to the North); the religious writer and Burma missionary Emily Chubbuk Judson, alias Fanny Forrester (1817–1854), who died in Hamilton, New York; the social reformer George Lippard (1822–1854), self-appointed "Supreme Washington" of the "Brotherhood of America," who developed Marxian ideas while Marx was still a schoolboy; the physician Henry Stuart Patterson (1815–1854), who, while "dying, eulogized the dead (Samuel G. Morton)"; the medico-legal expert Moreton Stillé (1822–1855), who authored with the lawyer Francis Wharton a textbook on medical jurisprudence; the plastic surgeon Thomas Dent Mütter (1811–1859), who, like the preceding three, died of tuberculosis in Philadelphia; and finally, one with many aliases (Geoffrey Crayon, Jonathan Oldstyle, Launcelot Wagstaffe, Friar Antonio Agapida), the renowned poet Washington Irving (1783–1859), who lived with, but did not die from, tuberculosis.

[9] These data were obtained by Mr. Royal A. Elfast, Jr. from the Massachusetts Division of Tuberculosis Control, and by Mr. William J. Kane, Chief, Vital Statistics, Boston City Health Department, and were taken from the collection of Dr. George Kahn, Chief, Bureau of Disease Control of the Boston Health Department.

[10] The Chicago series was contributed by Dr. Herman N. Bundesen, President of the Chicago Board of Health.

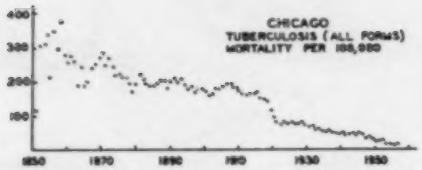

FIG. 15. The "German" peak is well indicated at the very beginning of the curve, and was probably the essential climax in Chicago. The Civil War itself caused no visible accident, but the early (1870) "Negro" peak is well formed, because the "Windy City" was a heavily used terminal of the underground railroad. Shortly after 1900 there is a "hill" which may qualify for the eponym of "Polish"; this is one of the few exceptions when Eastern European immigration was so numerous as to prevail in the death rate of certain metropolitan areas. Even the overlay disappeared after the post-World War I influenza dip, which coincided with a change in the immigration laws. *Source:* Chicago Board of Health (*see* footnote 10).

To this list, the South contributed the Alabama physician (and pupil of Velpeau) John Y. Bassett (1805–1851); the Louisville specialist in consumption William Adair McDowell (1795–1853), who had a famous controversy with Yandell on the subject of the curability of phthisis; the Virginian Thomas Hopkins Shreve (1808–1853), who died in Louisville where he had lived as a writer and editor; and the brilliant Nashville journalist John Leake Marling (1825–1856), who became United States Minister to Guatemala, but returned to die of tuberculosis in Nashville.

An industrial revolution was taking place in the North, while the South had developed a cotton planter aristocracy, based on slave labor. The discrepancy between these two factions resulted in the murderous Civil War (1861–1865), the control of public (federal) policy and the inflammatory political issue of slavery being at stake. The prolonged war years, and the willfully delayed reconstruction constituted an acute episode of urbanization which accelerated the course of the tuberculosis wave. As it happens, the Civil War deflection can seldom be identified, sometimes because the data are missing; it is best seen in the male curve from Providence, Rhode Island (*see* figure 28). A posthume effect of the War of the Rebellion was the appearance of a third tuberculosis climax, but this shall be discussed later. "During the 5 and ⅙ years (of war), 13,499 (0.61%) cases (of consumption) were reported among the white troops, and 5,286 (0.22%) died[11] . . . Among colored troops the proportions and figures were 1,331 (0.73%) cases and 1,211 (0.63%) deaths" (112). These data can best be amplified by stating that a Confederate Secretary of War and grandson of Thomas Jefferson, the frail George Wythe Randolph (1818–1867), died of tuberculosis; and a Union Secretary of War, John Aaron Rawlins (1831–1869), a former lawyer from the "lead city of the hills" (Galena, Illinois), whose wife had succumbed to the same disease in 1861, died also of tuberculosis.

[11] The favored treatment was one-half ounce of cod liver oil in one ounce of whiskey. Other "stimulants" highly recommended were brandy-punch, sherry wine, beer, and porter (112).

Many other noted persons died of tuberculosis during the war; for instance, the frontier painter Carl Wilmar (1828–1862), who was so sick at the end that he had to be lifted to the scaffold to complete his last work, the decoration of the courthouse in St. Louis; the psychiatrist Luther Vose Bell (1806–1862), who described Bell's disease (typhomania) and died of hemoptysis at Budd's Ferry, Maryland, while serving as medical director of a Union division on the Potomac; the physician Jedediah Vincent Huntington (1815–1862), who was also an Episcopalian minister and Catholic convert, as well as editor of Catholic proselytic papers; the "preaching woman," Achsa W. Sprague (1828–1862), who lived with, and died from, "scrofulous disease"; the beautiful, charming, and talented Emily Bradley Neal Haven (1827–1863), who edited for six years (after her husband's death) the Neal's *Saturday Gazette;* the promoter of Negro education, Myrtilla Miner (1815–1864), founder of Miner Teacher's College, who supported herself by clairvoyance and magnetism (and was also quite handy with a gun); the Congregational clergyman Russell S. Cook (1811–1864), who later sympathized with the Oxford movement and worked for the American Tract Society; the tuberculosis specialist Leonidas Marion Lawson (1812–1864), author of a textbook on phthisis pulmonalis (1861); the actress Mary Devlin Booth (1842–1865), sister-in-law of Lincoln's killer; the famous astronomer George Phillips Bond (1825–1865), to whom the Harvard College observatory was almost a family enterprise (he had lost a consumptive brother in 1841), and who is known for the discovery of the eighth satellite of Saturn (Hyperion) and for the memoir on the Donati comet (1858); and the celebrated Southern poet ("laureate of the Confederacy") Henry Timrod (1828–1867), who wrote the plaintive "Ode for the Magnolia Cemetery" ("There is no holier spot of ground / Than where defeated valor lies, / By mourning beauty crowned").

The relationship between transcendentalism and tuberculosis deserves special mention. Henry David Thoreau (1817–1862) had to overcome a phthisical episode when he retired for two years (1845–1847) to a hut beside Walden Pond, at Concord, Massachusetts; but he died of tuberculosis. Nathaniel Hawthorne (1804–1864) lived with the same disease for a longer time, yet it killed him in the end. Others, like the renowned Ralph Waldo Emerson (1803–1882), succeeded to achieve a cure. It could be that the interest of the transcendentalists in the Brook Farm Experiment ("plain living and high thinking") was prompted by medical advice; yet this is difficult to substantiate after a century.

By 1890, the Western Frontier had given way to the "Industrial Frontier," but only after it had provided inexhaustible material for innumerable sequences of best sellers, in print, as well as on the stage and screen. Although many tuberculous undertook Western trips in the hope of a cure, the disease is not too often mentioned in the various plots.[12]

The roster of noted tuberculous of that period includes the journalist, humorist, and actor, Charles Farrar Browne (1834–1867), remembered in "show biz" under the pseudonym Artemus Ward; the lawyer and historiographer Winthrop Sargent (1825–1870); the

[12] A few exceptions to this rule will be quoted from relatively recent moving pictures: a healed (post-traumatic) tuberculous was enacted by Glenn Ford in "The Violent Men;" in "Dawn at Socorro," Rory Calhoun played a consumptive who went to a Rocky Mountain town for treatment; and in "The Marauders," Dan Duryea portrayed a tuberculous patient with far advanced disease during a terminal psychotic episode. And then, of course, there is the case of the "weak lungs" of "Doc Holliday," who was Wyatt Earp's associate in Tombstone, and became involved in the famous episode at the O. K. Corral, perpetuated at the time of this writing through a regular television series.

naturalist William Stimpson (1832–1872), director of the Chicago Academy of Sciences, whose collections perished (together with those of his friend Robert Kennicutt) in the Chicago fire of 1871; Samuel Gregory (1813–1872), who was not a physician but founded in 1848 the Boston Female Medical School, the first of its kind in this country; the educator and mathematician John Fair Stoddard (1825–1873); the philologist Byron Caldwell Smith (1849–1877), college teacher at Jacksonville, Illinois, whose gracious letters were published in 1919 under the title of *Professor Ronsby Maldclewith's Love Life;* the Augustinian provincial Thomas Galberry (1833–1878), who became bishop of Hartford; the governor of Louisiana, Louis Alfred Wiltz (1843–1881), who took over when the federal troops left, and died of tuberculosis while still in office; the poet Sidney Lanier (1842–1881), lecturer of English Literature at Johns Hopkins and author of "The Marshes of Glynn."

Many physicians died of tuberculosis in the closing decades of the nineteenth century: the psychiatrist Samuel Worcester Butler (1823–1874); Jeffries Wyman (1814–1874), ethnologist, Hersey professor of anatomy at Harvard and friend of Agassiz; Stephen Purcell Bonner (?–1874), who acquired his tuberculosis while serving as a surgeon in the Civil War; the surgeon and scholar John Davies Jackson (1834–1875), who was the biographer of the pioneer ovariotomist, Ephraim McDowell; Richard Dennis Arnold (1808–1876), who was professor of medicine in the Savannah Medical College; Henry Sylvester Cheever (1837–1877), who was professor of materia medica, and later of physiology, at Ann Arbor; specialist in obstetrics and gynecology and anatomy professor at Woman's Medical College in Philadelphia, Emmeline Horton Cleveland (1829–1878), whose biographer stated that she was "possessed of much personal beauty"; Abram Paschal Garber (1838–1881), who was more of a botanist, and after whom were named a genus of thistles (*Garberia*), a palm (*Cocothrinax Garberi*), a morning-glory (*Convolvulus Garberi*), and a moss (*Fissidens Garberi*); William Clendenin (1829–1885), who was professor of anatomy and surgery in the Miami Medical College in Cincinnati; the professor of surgery and author of famous anatomical oil paintings, Frank Hastings Hamilton (1813–1886), who suggested skin grafting in 1847, published *Surgical Memoirs of the War of the Rebellion*, and made the extensively quoted "candid" statements after being consulted in the shooting of President Garfield; the neurologist James Stewart Jewell (1837–1887), founder and president of the American Neurological Association, and editor of the *Quarterly Journal of Nervous and Mental Diseases*; the leading New England surgeon, professor at Harvard, and author of a paper on the *Y* ligament of the hip joint, Henry Jacob Bigelow (1818–1890), who had tuberculosis in his younger years, but recovered, and is the only one in this group who did not die of tuberculosis; the ear, nose, and throat specialist, Ethelbert Carroll Morgan (1856–1891), author of a monograph on *Uvular Hemorrhage* and of wise dicta ("If you want good advice, go to friends; if you want to borrow money, go to strangers; and if you want nothing, go to relatives"); Alfred Lebbeus Loomis (1831–1895), who came from a family in which tuberculosis had "run rife," who was one of the early patients to rent a cottage at Paul Smith's in the Adirondacks, who advised Trudeau in opening what became Trudeau Sanatorium at Saranac Lake, and for whom the sanatorium at Liberty, New York was named; and the Johns Hopkins genito-urinary surgeon, James Brown (1854–1895), who was the first to catheterize a male urethra in a live patient, on June 8, 1893.

On the West Coast, the earliest peak was reached in the 1850s in San Francisco, while other cities, especially in southern California, traversed a flattened, rural climax a decade or more after completion of the first transcontinental rail-

road link (1869) between the two seaboards. Early tuberculosis death rates are not available for the states of Oregon and Washington, but it may be assumed that their coastal cities reached relatively low peaks (300–400 per 100,000) in the 1880s, or perhaps 1870s. In the meantime, the tuberculosis wave in New England had progressed to a very interesting point, well-described in 1889 by E. P. Hurd, a Newburyport, Massachusetts physician, who stated:

> As one of the descendants of an Eastern Township's pioneer, I witnessed much of this dire disease (tuberculosis) in my younger days. The malady appeared in both the acute and chronic form, and when once it had manifested itself, nothing could resist its progress. . . An interesting circumstance is that consumption is really becoming less and less frequent among the descendants of these early settlers, a fact to which I allude on the testimony of physicians long in practice in the Eastern Townships. Another gratifying circumstance is that consumption is more curable than it used to be . . . The relative infrequency of consumption among the descendants of families that have many generations been fixed to the soil, is a conspicuous fact. Such families, for instance, largely of British stock, as the Littles, the Lants, the Withingtons, the Lowells, the Woods, the Simpsons, the Pikes, the Moodys, the Knights, the Spaldings, the Stones, the Pettingills. I have inquired concerning the mortality records of all these families, and many more native to this region, and find consumption almost unknown for several generations. It is almost too much of a truism again to repeat that the strongest and fittest survive. This truth is exemplified in the history of consumption in New England. The native race is becoming more hardy, while immigration is furnishing the customary quota of deaths from consumption" (113).

The Racial Climaxes

After the Civil War, consumption—although decreasing among the descendants of the early (white) settlers in the North—maintained exorbitantly high death rates in the cities and was even increasing in the larger southern towns. This discrepancy was due to the fact that a new racial group had entered the picture.

The *emancipation* of the Negro slaves in the Rebel states, proclaimed by Lincoln in 1863, was a *symbolic* act. Further steps were accomplished by the lucrative partnership of "carpet-baggers," "scalawags," and "Union Leagues," during the famous period of "reconstruction," but even then emancipation was more *theoretical* than real. Instead of the expected "forty acres and a mule," the freed slave was offered a "black code," so that many preferred to continue (or to return) to work for their previous masters. The North was still waving its "bloody shirt" in 1877 when President Hayes withdrew the last federal troops from Louisiana and South Carolina, and these two states followed immediately in the pattern set everywhere else in the South: the Negro machines had been neutralized by "White Leagues," the "carpet-baggers" chased by "Knights of the White Camelia," and even "scalawags" were induced to join the "Ku Klux Klan." But the Negroes were no longer legally bound to a certain place of residence, and more and more of them achieved emancipation in a *practical* manner, by moving away from their guarded, *i.e.*, essentially rural, habitat. This acute urbanization carried an inflated price tag,[13] which included a staggering toll of tuberculosis mortality.

[13] It had been stated as early as 1827 that as soon as the "blacks" become free and move to the city, their mortality increases severely (115).

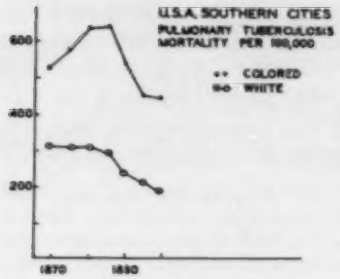

FIG. 16. These tracings would indicate the average time of the "Negro" peak. It was not possible to determine at this time what had been included in the category of southern cities. *Source:* Hoffman (114).

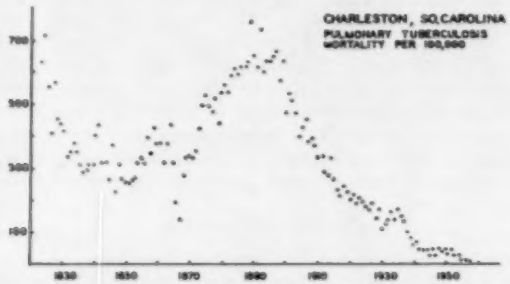

FIG. 17. The essential climax must have been surpassed shortly after 1800. Within the irregular variations at the beginning of the curve, there appears a deflection at the time of the Mexican War (1846–1848), which might have been obscured by the beginning of the "Irish" peak in the Boston curve (*see* figure 14), but which in Charleston is neatly separated. Most outstanding is the explosive "Negro" peak with its maximum around 1890. There is a noticeable accident in the 1930s (also seen in the New Orleans curve, *see* figure 13), which coincided with the growing industrialization of the South, as it was emerging from the depression. *Source:* Charleston County Health Department (*see* footnote 14).

The peak of tuberculosis mortality in the American Negro occurred around 1880 (figure 16). It was so high, especially when compared with the decreasing incidence among the remainder of the population, that it caused a significant hump (*third climax*) on many urban curves of the former Rebel states. Perhaps the most demonstrative tracing in this respect is that from Charleston, South Carolina[14] (figure 17). Not quite so explosive in appearance, but sufficiently evident, is the "Negro" peak in the curve of the District of Columbia[15] (figure 18).

Most of the southern cities missed the second (northern, midwestern, or German-Irish) peak. Conversely, in the northern and midwestern large towns,

[14] Dr. Gerald J. Specter, Public Health Educator of the Charleston County Department of Health, furnished this remarkable series of figures.

[15] The data have been obtained through the courteous cooperation of Mr. Howard West, Chief, Biostatistics and Health Education Division of the District of Columbia.

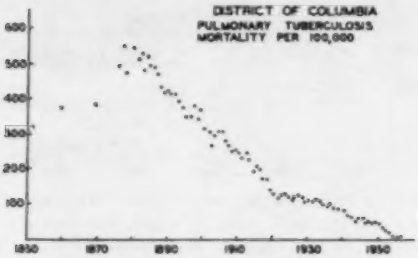

FIG. 18. Data prior to 1876 are taken from the decennial sampling of the Census Bureau. The "Negro" peak in the 1880s is clearly seen. The pronounced deceleration of the tuberculosis death rate following the post-war influenza dip may also be the result of continuous influx of Negro population, a fact which has also caused other public health problems in the capital. *Source:* Division of Biostatistics of the Government of the District of Columbia (*see* footnote 15).

the "Negro" peak occurred earlier than in the South, shortly after 1870, and was especially prominent in the large terminals of the underground railroad, for instance in Chicago (*see* figure 15), and in St. Louis[16] (figure 19). The deflections are much less conspicuous because northbound Negro migration, however substantial numerically in subsequent years, proceeded gradually, and never attained the sudden outburst which characterized the crowding of the southern cities by Negroes in the first decades after the Civil War.

In some of the urban areas of the South, the actual third peak may have occurred after 1880 or even 1890. Even so, by the turn of the century, the American Negroes had surmounted their tuberculosis climax, and since that time their death rates have declined continuously. Their situation at the epidemic stage of the wave is shown in the analysis by age and sex given in figure 20. This was maintained for a relatively long time after the climax had been surpassed (as newer contingents entered the acute phase of mass contamination and change of reactability). Nevertheless, it was only a matter of time (and deaths!) and phase, and they are now well advanced into the endemic stage of the wave (figure 21). Still, even today they offer a heavier contribution to the total tuberculosis death rates in the cities than the respective whites (figure 22).[17]

The first American (eastern) tuberculosis climax may also be called the "English" peak, while the second (northern) was a "German" (possibly part "Scandinavian") peak in the Midwest, and "Irish" in the East. The third (southern) was a "Negro" peak. Before the turn of the century, immigration had increased considerably (over one million yearly by 1890), and was predominantly of Southern European stock, at that time highly susceptible to tuberculosis, with

[16] The St. Louis data were obtained in part from Dr. R. J. Schurter, Supervisor of the Communicable Disease Control Division of the City Department of Public Welfare.

[17] The rates for figure 21 have been contributed by Miss Lillian Guralnick from the National Office of Vital Statistics. The Louisville series in figure 22 has been obtained through the courteous offices of Mr. Irving H. Levy, Director of Vital Statistics of the respective City-County Department of Public Health.

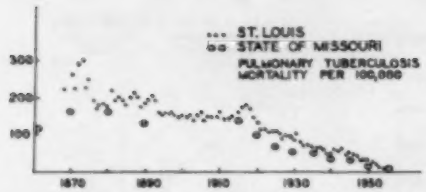

FIG. 19. The pronounced deflection in the post-Civil War period is an early "Negro" peak. Otherwise, the curve is not very "urban," which is in line with the gradual development of the city. Interesting is the difference in response to World War I and II. *Source:* St. Louis Department of Public Welfare (*see* footnote 16) and National Office of Vital Statistics.

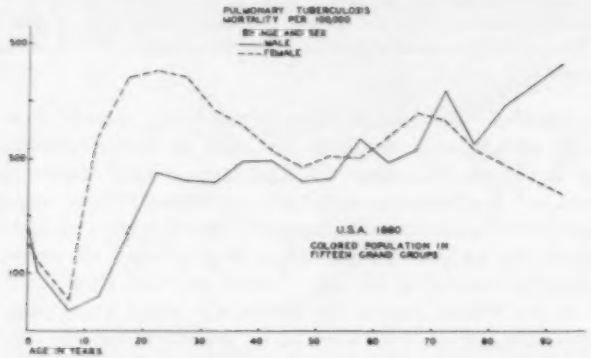

FIG. 20. The analysis by age and sex of tuberculosis mortality among Negroes in 1880 reveals an epidemic type of curve (compare with figure 4). *Source:* Billings (88).

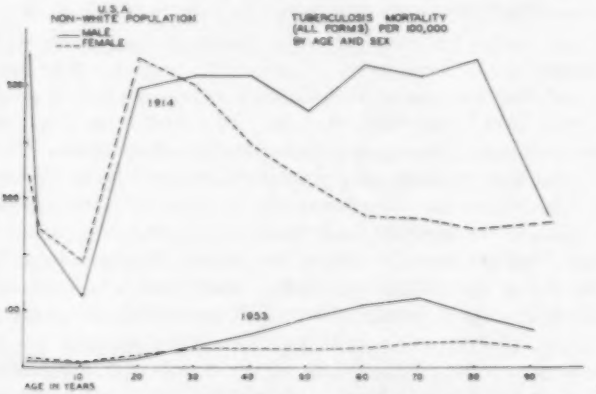

FIG. 21. In 1914 there was still a definitely epidemic type of tracing, but in 1953 the ethnic groups then tabulated as non-white (mainly Negro, American Indian, Chinese, and Japanese) were comfortably within the advanced stages of the tuberculosis wave. Deaths occurring among persons of Mexican and Puerto Rican origin are included with the white group. *Source:* National Office of Vital Statistics (*see* footnote 17).

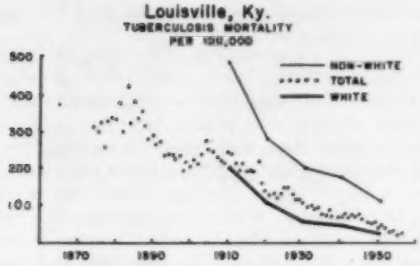

FIG. 22. The "Negro" peak is quite prominent. There is a surprisingly well seen "Indian" (?) peak after 1900. In addition, this graph demonstrates the contribution of the non-whites to the total tuberculosis death rate. *Source:* Louisville City-County Health Department (*see* footnote 17).

the exception of the Jewish, who at all times (at least whenever differential rates were obtainable) displayed a remarkable degree of lesser reactability and therefore lesser tuberculosis death rates than the surrounding gentiles. As a rule, the import of reactable persons was insufficient to outnumber the fast-growing immunity of the numerically larger American-born population. Perhaps closest to a peak came the "Polish" hill after 1900 in the Chicago tracing (*see* figure 15). Instead of Italian, Ukrainian, Greek, or Roumanian peaks, many of the metropolitan curves contain segments of "Southern and Eastern European" overlay or deceleration, i.e., a slowing down of the decrease of tuberculosis mortality, proportional to the number of foreign-born. A similar situation occurred on the West Coast with immigrants of Asiatic stock. There was however a fourth tuberculosis peak in the United States, the "Indian" climax.

The problem of tuberculosis among American Indians has received considerable attention in the literature. A frequently heard *leit-motif* was that they were initially an over-all healthy, and phthisiologically "virgin" population, and that most of their present ills, including consumption, had been brought upon them by the European conquest. When the first settlers landed, there was an estimated total of 850,000 Indians within the boundaries of what is now the United States, while only about half that number exist today. Other statistics were also boldly displayed to point out that the remaining Indians would soon perish unless something were done about it. Prior to 1900, a few writers even intimated that the "conquerors," after killing so many Indians in armed encounters and depriving the remainder of their lands, were perpetuating a willful neglect, so that it might complete the massacre and exterminate the Indian survivors.

In point of fact, as previously stated (115a, 70), consumption had existed among the Indian tribes in the pre-Columbian era, and certainly in the seventeenth century, prior to the first "white" peak. The contrary opinion can be traced back to Benjamin Rush (1744–1813), who rejected the accounts of the Canadian historians Charlevoix and LaHontan in the preamble to his oft-quoted statement (116) that "it (consumption) is unknown among the Indians of North-America." The origin of Rush's information was a personal communication from Major General Edward Hand (1744–1802), remembered as one of the handsomest men in the Continental Army, who had studied

the Indians during his residence as a surgeon at Fort Pitt (later Fort Duquesne), located near the site occupied by Pittsburgh.[18]

Rush was contradicted at a very early date, for instance, in the memoirs of a white man who had been held captive by the Indians (117), and in the writings of some of his own pupils (118, 119). Very impressive was the description of the ravages which occurred in the family of the Seneca Indian chief, Red-Jacket (1750?–1830), as given by Francis: "The celebrated chief, Red-Jacket, in an interview I had with him at a reservation near Buffalo, in September 1823, gave me the particulars of the cases of no less than seventeen of his relatives (including, I think, ten or eleven of his own children) who had died of pulmonary consumption. He was quite descriptive in his statement, and seemed sufficiently qualified to make a number of very fair distinctions in relation to this matter" (120). Glisan (121) mentioned that consumption becomes a problem only when the Indians are restrained in camps or reservations. Similar statements are found in numerous subsequent papers (122–124).

The Indians in the United States are all but an homogenous group. Their tuberculosis history is therefore a local, rather than a general, phenomenon. Multiple, small peaks were scattered throughout the country. They were determined by the degree of urbanization to which the respective Indian community was exposed. As a rule, the smaller groups, mainly in the East, lagged fifty to sixty years behind the remainder of the population, while further West (and especially in the Southwest), the distance was only thirty to forty years, perhaps because of the mixed origin of the existing so-called white stock. To comprehend any given situation (for instance, that of the well-studied Navajos in Arizona), one must analyze the various specific conditions of the group. Obviously, a nation-wide average can seldom apply to each of its components. However, for convenience in presentation, we may think of the Indians as a whole and, as such, their peak of tuberculosis mortality occurred in North America between 1900 and 1910[19] (figure 23), although even as recently as 1940 some of the reservations still displayed the epidemic type of curve when analyzed by age and sex.

This fourth, southwestern (far western?) or "Indian" peak can be identified in the tracing of El Paso, Texas[20] (figure 24), which bears a strange resemblance to the Indian spike in figure 23. The tracing of San Francisco[21] (figure 25) shows

[18] This information was provided by Miss Mary E. Grinnell from the Reference Section of the National Library of Medicine. Miss Ellen G. Mayeux, from the same Section, and especially Dr. Dorothy M. Schullian, Director of the Historical Branch of the same library in Cleveland, assisted in procuring some of the early Americana needed in this paper. Credit is also given to Mr. John M. Weaver of the Circulation Section.

[19] The data since 1940 have been provided by Miss Helen Hollingsworth, Chief, Program Analysis, Division of Indian Health, and originate from special tabulations of the National Office of Vital Statistics.

[20] This graph has been drawn from data furnished by Mrs. Elisabeth Marcus, R.N., of the Tuberculosis Control Division of the City-County Health Department of El Paso, who went to such extremes as to read every death certificate from 1887 until 1910, for which we are certainly grateful.

[21] This valuable run, the longest on the West Coast, was obligingly assembled by Dr. Ellis D. Sox, Director of the City-County Department of Health of San Francisco.

only a heavy overlay in the area of the Indian peak. This can be explained by the massive immigration of Central American stock, known to contain a substantial Indian background, although Asiatic elements must have contributed to a great extent to this overlay. A similar appearance is found in the tracing of

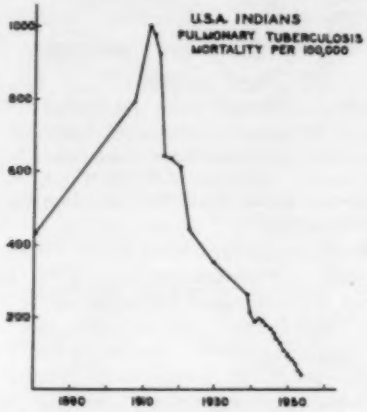

FIG. 23. This tracing unites points inscribed from data which are so heterogenous in regard to coverage, provenience, and method of collection, that the simple fact of having them included on the same sheet of paper must appear as a blasphemy to any trained statistician. However, since they serve our purpose, the graph has not been deleted. *Source:* Billings (88), Hrdlicka (115a), Reifel (125), and Division of Indian Health (*see also* footnote 19).

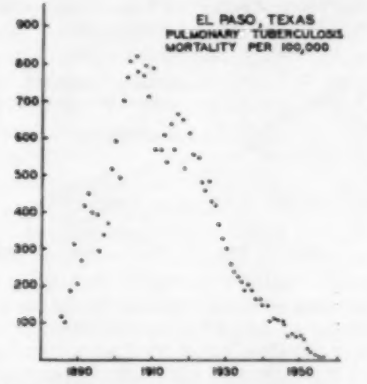

FIG. 24. This spire, which can almost be superimposed on that in figure 22, was produced by the massive influx into El Paso of population from south of the border. It is the most typical example of the fourth (or southwestern) peak in the United States, and qualifies also for the terminology of "Indian" peak because the Central American Indian component in Mexican ancestry is well documented. *Source:* El Paso City-County Health Department (*see* footnote 20).

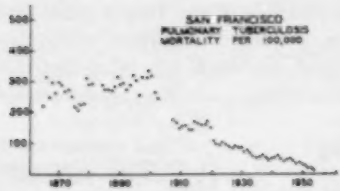

FIG. 25. The "Negro" peaks of 1870 and 1880 are seen, and the latter continues imperceptibly with the "southwestern" hill, which spikes after 1900. In San Francisco there is always a large percentage of recent immigrants, especially of Asiatic origin, and these participated heavily in "overlaying" the above described "hill." A similar explanation would account for the prominent deflection of World War I, while the immigration laws have prevented this occurrence during World War II. *Source:* San Francisco City-County Health Department (*see* footnote 21).

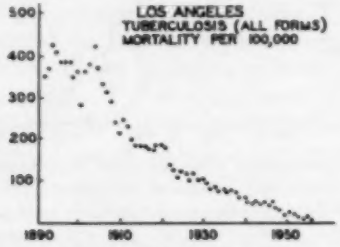

FIG. 26. Only the aftermath of a "Negro" peak is seen in the 1890s, while the "southwestern" spire must have an Asiatic component. The deflection of World War I and a similar but faintly indicated one in World War II are the only other accidents of the curve. *Source:* Los Angeles Health Department (*see* footnote 22).

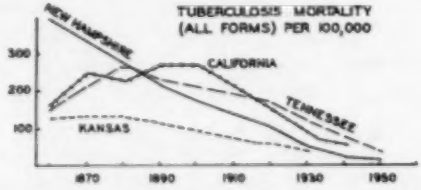

FIG. 27. This is a graphic summary of the four U. S. A. peaks of tuberculosis mortality as they appear in the decennial samplings obtained by the Census Bureau since 1850 (the 1850 figures were too fragmentary, and, with few exceptions, have not been utilized in this paper). The *first* (eastern or "English") peak occurred in New Hampshire probably about 1860. The *second* (of which the midwestern or "German" segment is shown here) obviously rural type of climax can be seen at the beginning of the Kansas curve. The *third* (southern or "Negro") peak is demonstrated in the figures of Tennessee. The *fourth* (southwestern or "Indian") hill is visible in the California tracing, which displays also an earlier deflection (probably post-Civil War and/or early "Negro" peak). *Source:* National Office of Vital Statistics.

Los Angeles[22] (figure 26). In the curves of the cities placed along the pathways of the Mexican immigrants toward the methopolitan areas, the overlay is less well seen and its after-effect—the persistently higher mortality in the southwestern states as compared with the remainder of the country (126)—tapers off gradually. However, in spite of this considerable progress, even today, Mexicans, Negroes, and Indians prevail numerically in American tuberculosis sanatoriums. Furthermore, the last group to make its escape from the epidemic stage of tuberculosis is that of the Eskimo population in Alaska.

A summary of the four peaks can be found in the curves of four representative states (figure 27), quite expressive, notwithstanding the relatively incomplete data on which they are based (decennial sampling prior to 1900).

Among the notable victims of tuberculosis after the turn of the century, one may list Amos Griswold Warner (1861–1900), professor of economy at Stanford and author of *American Charities*, a classic in applied sociology; Stephen Crane (1871–1900), who wrote *The Red Badge of Courage* while a war correspondent in Cuba; Henry Harland (1861–1905), creator of polished prose, exemplified by *The Cardinal's Snuff Box*; the lyric poet, Paul Lawrence Dunbar (1872–1906), son of an escaped Negro slave and author of *Slow through the Dark* ("Slow moves the pageant of a climbing race"); William Garrott Brown (1868–1913), author of *Some Confessions of a T. B.*; Adelaide Crapsey (1878–1914), who composed cinquains for the initiates, and referred to the graveyard as "Trudeau's garden" ("And in ironic quietude who is / The despot of our days and lord of dust?"); the painter Frederic Oakes Sylvester (1869–1915), who had his body cremated and the ashes thrown into his beloved Mississippi; Hermanes Barkulo Duryea (1863–1916), remembered for his turfy exploits (he won $250,000 at the 1914 Epsom Derby with the famous horse Durbar II); Christopher Mathewson (1880–1925), baseball player with the Giants, then part-owner of the Boston Braves; the physical anthropologist Louis Robert Sullivan (1892–1925); and the professor of English at Columbia and at Hunter, Roy Floyd Dibble (1887–1929).

The list of tuberculous physicians begins with William Phipps Munn (1864–1903), a former genitourinary man who became health officer in Denver, a change of climate which did not prevent his death from tuberculosis; Augustus Palmer Dudley (1853–1905), a known gynecologic surgeon, whose first wife, Susie Stephens, also died of tuberculosis; the Canadian John Hewetson (1867–1910), author of the famous preparations of neuropathologic specimens (medulla, pons, and midbrain of newborn children) at Johns Hopkins; Thomas Almond Ashby (1848–1916), founder of the *Maryland Medical Journal* and author of a textbook on gynecology; Samuel Max Brickner (1867–1916), editor of the humorous *Medical Pickwick*, who was the "peak-faced and suffering piper" described in Stevenson's lines; Jonathan Bailey Rogers (1886–1922), the pathologist who was infected while investigating the contagiousness of moist sputum sprayed on guinea pigs; the tuberculosis specialist and Rhodes fellow McDugald McLean (1886–1922); the tuberculosis specialist of the U. S. Army, George Ensign Bushnell (1853–1924); Harry Gilmore Carter (1886–1926), the (white) director of the Piedmont Sanatorium for Negro patients in Virginia; Bertram Howard Waters (1867–1927), at one time chief of Loomis Sanatorium; John Archibald Smith (1877–1928), who worked in the public health field; and

[22] These figures were provided by Mr. James B. Swayne, Director, Statistics and Analysis Division of the Los Angeles Health Department.

Henry Robert Murray Landis (1872–1937), professor of clinical medicine in the University of Pennsylvania, who wrote with George W. Norris the famous *Textbook on Diseases of the Chest*.

In the case histories of several physicians, tuberculosis had been only an interlude, but the study of the disease had remained as an avocation for the former patient, as happened to Henry Sewall (1855–1936); to Lawrence Francis Flick (1856–1938), in whom the prelude lasted for almost ten years, and who became one of the founders of the National Tuberculosis Association and author of a detailed historical study of tuberculosis; to the brilliant Allen Kramer Krause (1881–1941), former editor of the *American Review of Tuberculosis*; to John Alexander (1891–1954), who pioneered the surgical treatment of tuberculosis and published the first textbook on this subject in English; and to David Russell Lyman (1876–1956), the well-known director of Gaylord Farm Sanatorium in Connecticut.

A special mention is deserved by the Saranac Lake team, initiated by Edward Livingston Trudeau (1848–1915) and continued by Lawrason Brown (1871–1937), both of whom lived with, and died from, tuberculosis. Conversely, all other members of the "team," mentioned below, had tuberculosis at some time during their lives, but did not die from it. For instance, the promising Robert Childs Paterson (1878–1921) was killed by the bullet of a deluded patient; Homer L. Sampson (1880–1945), who was not a physician, became an expert in roentgenographic interpretation and co-author of a textbook on intestinal tuberculosis. Others were: Leroy U. Gardner (1888–1946), who was an authority on silicosis; Fred Henry Heise (1883–1946), who succeeded Lawrason Brown as director at Saranac in 1929 and is perhaps best remembered for his *1000 Questions and Answers on TB*, first issued in 1935; William Charles White (1874–1947), who resigned his position as professor of neuro-anatomy at Indianapolis to come to Saranac Lake because of his tuberculosis, but later went into public health work in Washington; Edward R. Baldwin (1864–1947), who was mainly a biologist and bacteriologist, although generally regarded as the spiritual successor of Trudeau; and certainly not the least, Strachimer A. Petroff (1883–1948), the mechanical genius who came from Bulgaria to the United States for a medical tour, broke down with tuberculosis, landed at Saranac Lake, stayed there for the rest of his life, and developed, among other things, the famous medium which carries his eponym.

The Beginning of the End

During the 1920s, ten billion dollars was spent on improving highways in the United States, and a sharp increase occurred in the production of automobiles. The resultant perpetual motion has become so much a part of American life that a radio commentator (Alex Dreier) proudly refers to himself as "the man on the go." Tuberculosis took free advantage of this actively boiling melting pot, and the natural selection of reactable individuals made huge strides, well demonstrated by the subsequent, spectacular decline of its death rate.

The first Adirondack Cottages were opened in 1884; the Trudeau Sanatorium was officially inaugurated at Saranac Lake in 1904. It maintained throughout its existence the initially devised policy "To cure sometimes, to relieve often, to comfort always." Its closing, late in 1954 (in 1957, it was purchased by the American Management Association and converted into the "world's largest!" resident training facility for business executives), marked the *beginning of the end*, and many sentimental pages were dedicated to the passing of an era. A special

editorial appeared in the *American Review of Tuberculosis* (127), and not too long afterwards, this publication added to its title the words *and Pulmonary Diseases*. Even the American Trudeau Society considered a possible change of name.

World War I and the subsequent influenza epidemics (128) were followed by a steep decline in tuberculosis mortality, and a similar (though less steep) decrease can be recognized after the (also less visible) hump caused by World War II. If the inherent fluctuations of the rate are disregarded, its speed of decrease seems to be slowing down in the last fifty years. This is expected because, in accordance with its exponential characteristics, the logarithmic curve can never reach the base line.[23] There shall always be a few cases of tuberculosis, as there are a few cases of leprosy. It suffices to have the curve reach the point where tuberculosis ceases to be a public health problem and becomes a medical curiosity, relegated to the category of single case reports.

[23] The zero level could be attained "beyond the horizon," like the meeting point of the two parallel lines, described by a relativistic but anonymous varsity minstrel: "There is a place apart / Beyond the solar ray, / Where the two lines can meet / In an informal way."

To be concluded in the next issue of the REVIEW

IN VITRO AND IN VIVO EFFECT OF ANTIMICROBIAL AGENTS ON ATYPICAL MYCOBACTERIA[1,2]

WILLIAM STEENKEN, JR., MARJORIE M. SMITH, AND V. MONTALBINE

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INTRODUCTION

Prior to the use of antimicrobial therapy in tuberculosis, sputum was cultured for diagnosis of the disease only if repeated concentrated smears were negative for acid-fast organisms. The sputum of patients with obvious disease that was positive on microscopy was seldom cultured. Since the discovery of antimicrobial agents and their treatment of tuberculosis, however, the sputum of virtually all patients is cultured. This is done to determine the drug susceptibility of the organisms harbored by the patients in order to institute a proper course of drug therapy. This procedure (mass culturing) has brought to light the incidence of atypical mycobacteria observed today. Since these atypical mycobacteria are undoubtedly disease entities, several questions arise: (*1*) What antimicrobial agent, or combination of agents, can be used effectively in treating patients having such mycobacteria associated with their disease? (*2*) During antimicrobial therapy, do the atypical mycobacteria lose their drug susceptibility and, if so, how rapidly?

It is the purpose of the present report to present the results of the effect of certain antimicrobial agents upon an infection produced in mice by drug-susceptible atypical acid-fast mycobacteria isolated from the sputum of 4 patients before therapy. Subsequently, the same organisms were isolated from the patients' resected lung lesions.

The results of an infection induced in mice by isoniazid- and streptomycin-resistant atypical acid-fast mycobacteria (strain Brownell) and treated with isoniazid and streptomycin will be discussed.

MATERIALS AND METHOD

The organisms selected for study were those most commonly isolated from patients having atypical mycobacteria associated with their disease, and from whom tubercle bacilli have never been isolated. Two of the strains, Brownell and Coffey, were discussed in a previous publication (2). These strains met the following criteria:

Colorless when grown in the dark, yellow when grown in the presence of light, or exposed to light at intervals during the growth period; good growth at 37°C. in seven to twelve days, moderate at 33°C. in sixteen days, and slight at room temperature in twenty-one days; poor "cord formers"; negative neutral red; excessive catalase activity; negative niacin; moderate pathogenicity for mice when inoculated intravenously, avirulent for guinea pigs

[1] From the Trudeau Laboratory of the Trudeau Foundation, Inc., Saranac Lake, New York.

[2] This study was supported in part by a research grant (E36 C11) from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, U. S. Public Health Service.

by the subcutaneous route, very slight virulence when inoculated intracardially; highly resistant to PAS and pyrazinamide.

Six drugs[3] were chosen for therapy: cycloserine, amithiozone, streptomycin, thiocarbanilide (SU 1906), thiocarbanidin (Y 9525), and isoniazid. Their selection from a large number of agents tested was based on their superior action *in vitro* against the photochromogenic atypical mycobacteria (3).

Observations

Therapy Experiment in Mice Infected with Drug-Susceptible Strains of Atypical Mycobacteria

One hundred and seventy-two white mice (CF1 strain, average weight 25 gm. each) were infected intravenously with 4 mg. (dry weight) of atypical mycobacteria from an eight-day-old culture on Steenken and Smith medium; 43 with strain Brownell, 43 with strain Coffey, 43 with strain Fobes, and 43 with the Hunt strain. Each group was divided as follows:

Seven animals acted as controls. Six were treated with cycloserine, 5 mg. or 200 mg. per kg. per day by injection; 6 with amithiozone, 0.25 mg. per 100 ml. in diet or 500 mg. per kg. per day; 6 with streptomycin, 2.5 mg. or 100 mg. per kg. per day by injection; 6 with thiocarbanilide (SU 1906), 0.25 mg. per 100 ml. in diet or 500 mg. per kg. per day; 6 with thiocarbanidin (Y 9525), 0.25 mg. per 100 ml. in diet or 500 mg. per kg. per day; 6 with isoniazid, 0.1 per cent in diet or 200 mg. per kg. per day. Treatment was begun immediately after infection and was continued for thirty-one days. All survivors were sacrificed on the thirty-first day. The results of this experiment are recorded in table 1.

The analysis in table 1 shows that these strains of atypical mycobacteria did not produce equivalent disease in the control animals, even though the cultures were all of the same age and met identical criteria in their selection. Cycloserine and amithiozone had little effect in the dosage used despite the fact that they were active *in vitro*. Streptomycin and SU 1906 had limited effect against the Brownell and Coffey strains, whereas isoniazid and Y 9525 showed fair effect against Brownell and good effect against the Coffey and Fobes strains of mycobacteria. The Hunt strain was quite refractory to all drugs.

The number of animals with gross kidney disease may be seen in table 2. The numerator denotes the number of animals that had gross kidney disease, and the denominator the number of animals comprising each group. It is obvious from table 2 that kidney disease was not a consistent finding in all control mice. Virtually all of the treated animals were free of gross kidney disease, except the animals infected with the Hunt and Fobes strains and treated with streptomycin.

The number of animals that died of their disease, as well as the number of animals that were sacrificed on the thirty-first day to terminate the experiment, are given in table 3. It may be seen that the Brownell strain produced the most lethal infection with 100 per cent mortality in the controls in twenty days. The Hunt and Fobes strains each produced a 57 per cent mortality in ten and nineteen days, respectively, whereas the Coffey strain had zero mortality for the

[3] Cycloserine was kindly supplied by Eli Lilly & Company, Indianapolis, Indiana; amithiozone by Schenley Laboratories, Inc., New York, New York; isoniazid and streptomycin by Chas. Pfizer & Company, Brooklyn, New York; thiocarbanilide (SU 1906) by Ciba Pharmaceutical Products Company, Summit, New Jersey; and thiocarbanidin (Y 9525) by Parke, Davis & Company, Detroit, Michigan.

TABLE 1

GROSS LUNG DISEASE IN DRUG-TREATED ANIMALS INFECTED WITH ATYPICAL MYCOBACTERIA

Groups	Gross Lung Disease*			
	Brownell	Coffey	Hunt	Fobes
Controls	3.9	2.5	2.3	1.6
Cycloserine, 5.0 mg., 200 mg./kg./day	3.4	2.0	2.1	1.3
Amithiozone, 0.25% diet, 500 mg./kg./day	3.1	2.4	2.6	1.0
Streptomycin, 2.5 mg., 100 mg./kg./day	2.4	0.6	2.3	1.7
Thiocarbanilide (SU 1906), 0.25% diet, 500 mg./kg./day	2.0	1.1	2.0	1.2
Thiocarbanidin (Y 9525), 0.25% diet, 500 mg./kg./day	1.7	0.3	2.3	0.7
Isoniazid, 0.1% diet, 200 mg./kg./day	1.5	0.0	1.7	0.2

* Average disease, based on score of 0 to 4+.

TABLE 2

GROSS KIDNEY DISEASE IN DRUG-TREATED ANIMALS INFECTED WITH ATYPICAL MYCOBACTERIA

Groups	Gross Kidney Disease			
	Brownell	Coffey	Hunt	Fobes
Controls	4/7	0/7	2/7	3/7
Cycloserine	2/6	0/6	1/6	1/6
Amithiozone	0/6	0/6	0/6	0/6
Streptomycin	1/6	0/6	6/6	5/6
Thiocarbanilide (SU 1906)	0/6	0/6	0/6	0/6
Thiocarbanidin (Y 9525)	0/6	0/6	0/6	0/6
Isoniazid	0/6	0/6	1/6	0/6

TABLE 3

ANIMALS WHICH DIED OR WERE SACRIFICED ON THIRTY-FIRST DAY

Groups	Mortality			
	Brownell	Coffey	Hunt	Fobes
Controls	7/7	0/7	4/7	4/7
Cycloserine	6/6	0/6	5/6	5/6
Amithiozone	1/6	0/6	1/6	1/6
Streptomycin	0/6	0/6	0/6	0/6
Thiocarbanilide (SU 1906)	1/6	0/6	0/6	0/6
Thiocarbanidin (Y 9525)	0/6	0/6	0/6	0/6
Isoniazid	0/6	0/6	0/6	0/6

Numerator—deaths.
Denominator—number of animals in each group.
All survivors were sacrificed 31 days after infection.

thirty-first-day survival period. It will also be noted that the animals infected with strains Brownell, Hunt, and Fobes and treated with cycloserine all died early in contrast to those animals infected with the Coffey strain and all other treated groups of animals. Such early deaths are common observations in animals with progressive disease being treated with an ineffective toxic drug.

Emergence of Drug-resistant Microorganisms in Vitro

Each of the four strains of atypical mycobacteria used in this study, as well as the H37Rv strain, was grown in the presence of cycloserine, amithiozone, streptomycin, thiocarbanilide (SU 1906), thiocarbanidin (Y 9525), and isoniazid. Transfers of the cultures were made every fourteen days to tubes of 7H9 solid medium, containing increasing concentrations of the respective drug. Stock solutions of SU 1906 and Y 9525 were prepared, each containing 40 mg. per ml. in dimethylacetamide, from which serial dilutions in the medium were made. The results are recorded in figure 1.

In figure 1 are represented the results of the growth of the four strains of atypical mycobacteria and the H37Rv strain of tubercle bacilli, when grown in the presence of the six drugs. The solid line is a composite of the growth of the atypical strains, unless otherwise shown by the dotted line. The dash-dot line in all cases indicates the growth of the H37Rv strain. A study of the graphs will show that the atypical mycobacteria lose their susceptibility to cycloserine, amithiozone, SU 1906, and Y 9525 at about the same rate and to the same degree as the human H37Rv strain; whereas the atypical strains, when grown in the presence of streptomycin or isoniazid, lose their susceptibility more rapidly and to a greater degree than the H37Rv strain.

Therapy Experiment in Mice Infected with Streptomycin and Isoniazid-susceptible and -resistant Atypical Mycobacteria

The Brownell strain was made resistant *in vitro* to 100 γ of isoniazid per ml. and 200 γ of streptomycin per ml. by serial transfer in drug containing Tween®-albumin medium. Seventy CF1 mice were infected: 30 with microorganisms susceptible to isoniazid and streptomycin, 20 with isoniazid-resistant organisms, and 20 with streptomycin-resistant organisms. The 30 mice infected with the organisms susceptible to isoniazid and streptomycin were subdivided into three groups of 10 each. One group served as nontreated controls; the second was treated with isoniazid, 0.1 per cent or 200 mg. per kg. per day in diet; and the third group was treated with streptomycin, 2.5 mg. or 100 mg. per kg. per day by intramuscular injection.

The 20 mice that were infected with isoniazid-resistant organisms were divided into groups of 10 each; the first acted as nontreated controls and the second was treated with isoniazid, 200 mg. per kg. per day. The remaining 20 mice infected with streptomycin-resistant organisms were likewise divided into two groups, 10 nontreated controls and 10 treated with streptomycin, 100 mg. per kg. per day. Treatment was started immediately after infection and continued for thirty-one days. All survivors were sacrificed on the thirty-first day. The results of the experiment are recorded in table 4.

It may be seen in table 4 that the susceptible strain produced the most lethal infection, with 60 per cent mortality in the controls in twenty-four days. Those infected with streptomycin-resistant organisms had a 40 per cent mortality in

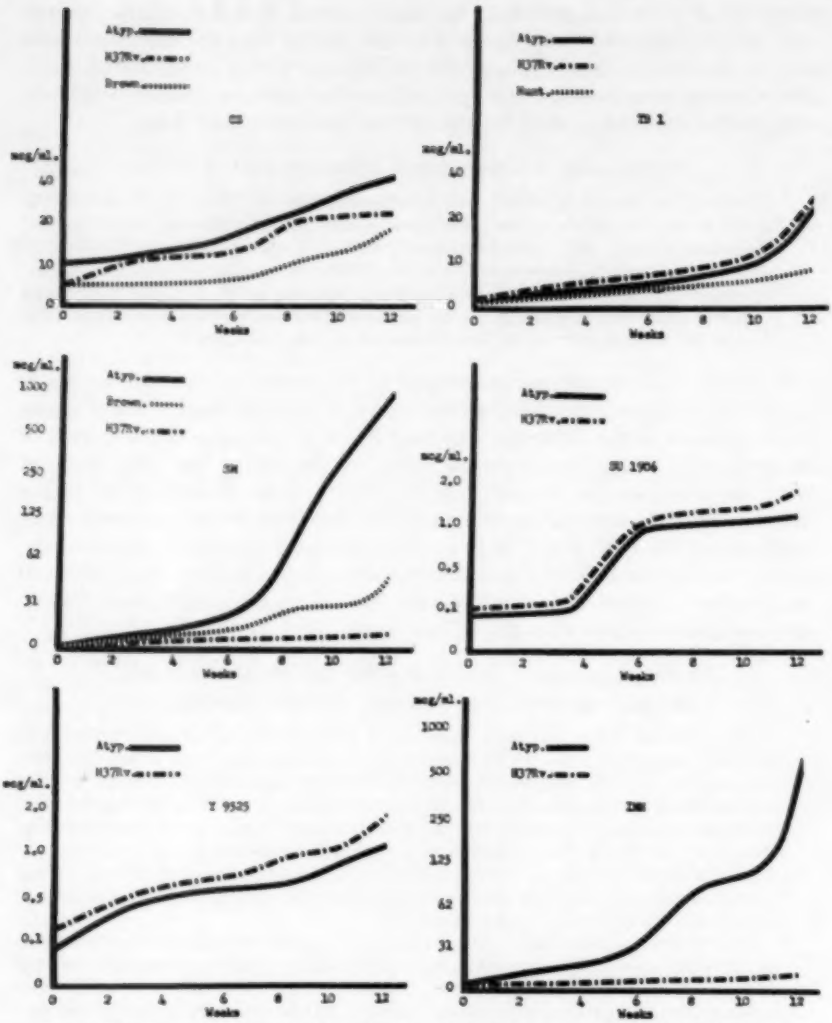

FIG. 1. Results of the growth of four strains of atypical mycobacteria and H37Rv strain of tubercle bacilli, grown in the presence of six drugs.

CS—cycloserine
TB 1—amithiozone
SM—streptomycin
SU 1906—thiocarbanilide
Y 9525—thiocarbanidin
INH—isoniazid

TABLE 4

RESULTS OF THERAPY IN MICE TREATED WITH STREPTOMYCIN- AND ISONIAZID-SUSCEPTIBLE MYCOBACTERIA

Brownell	Groups	Number of Animals in Each Group	Gross Disease		Mortality
			Lungs	Kidneys	
Susceptible to 2.0 γ of streptomycin per ml. 1.0 γ of isoniazid per ml.	Control	10	3.6	2.2	6 deaths in 24 days 4 sacrificed 31st day
	Treated, isoniazid*	10	1.0	0.2	10 sacrificed 31st day
	Treated, streptomycin†	10	1.5	0.1	10 sacrificed 31st day
Resistant to 100 γ of isoniazid per ml.	Control	10	2.7	2.8	1 death 23rd day 9 sacrificed 31st day
	Treated, isoniazid*	10	2.9	3.4	10 sacrificed 31st day
Resistant to 200 γ of streptomycin per ml.	Control	10	3.3	2.4	4 deaths in 23 days 6 sacrificed 31st day
	Treated, streptomycin†	10	3.3	2.3	10 sacrificed 31st day

* 0.1% in diet or 200 mg. per kg. per day.
† 2.5 mg. intramuscularly or 100 mg. per kg. per day.
Scoring disease same as in table 1.

twenty-three days, and those infected with isoniazid-resistant organisms had a 10 per cent mortality in twenty-three days. It will also be noted that the mice infected with the susceptible strains responded well to both streptomycin and isoniazid, whereas the mice infected with isoniazid- and streptomycin-resistant organisms did not respond to therapy. There is also some indication that the isoniazid-resistant organisms may be less virulent than the isoniazid-susceptible and the streptomycin-resistant strains.

DISCUSSION

Very little has appeared in the literature on the subject of antimicrobial therapy in humans or in the experimental animal infected with acid-fast atypical mycobacteria. In consequence, this study was undertaken to determine whether there is a correlation between the activity of a drug selected because of its superior action *in vitro* on atypical mycobacteria and the action of the drug upon an infection induced in a susceptible host (mouse) with these organisms. The atypical mycobacteria used in the experiment were selected because they are the most common in the group to be found associated with pulmonary disease. They also met certain criteria and were capable of producing progressive disease in mice, when inoculated intravenously. Appropriate methods of culture or animal passage should be established for maintaining the virulence

of freshly isolated strains of atypical mycobacteria. The necessity for such procedures became apparent while determining the infecting dose for mice of the various strains used in this experiment. Without question these strains have lost considerable virulence for mice since they were first isolated from the human host. The variation of atypical strains in their susceptibility to antimicrobial therapy, as shown in this report, is in direct contrast to the uniformly good results obtained in mice infected with heterologous strains of human tubercle bacilli, when treated with effective drugs.

Cycloserine, which has little or no influence upon a tuberculous infection in mice or guinea pigs, does have a limited effect in rabbits, monkeys, and humans. Some beneficial results might likewise be found in animals other than mice infected with atypical acid-fast mycobacteria, as well as in humans who have such microorganisms associated with their disease.

The atypical mycobacteria lose their drug susceptibility *in vitro* more readily than the H37Rv human strain of tubercle bacilli to streptomycin and isoniazid, whereas the loss of drug susceptibility is about the same for atypical organisms and H37Rv strains of organisms to cycloserine, amithiozone, SU 1906, and Y 9525. These findings would suggest the advisability of immediate use of multiple-drug therapy in patients, especially in those patients with cavity and atypical mycobacteria associated with their disease, in order to prevent or delay the emergence of drug-resistant organisms.

Summary

Four strains of photochromogenic mycobacteria produced disease in mice when inoculated intravenously. Cycloserine and amithiozone had virtually no effect upon an infection produced by all four strains. Streptomycin and thiocarbanilide (SU 1906) had limited effect against two of the strains, whereas isoniazid and thiocarbanidin (Y 9525) had a fair effect against one and a good effect against two others. One of the strains was quite refractory to all drugs. Mice infected with a strain resistant to streptomycin and isoniazid did not respond to therapy when treated with the drug to which the organisms were resistant. Atypical mycobacteria, like human tubercle bacilli, when grown in the presence of subinhibitory concentrations of a drug, lose their drug susceptibility.

Sumario

Efecto In Vitro e In Vivo de los Compuestos Antimicrobianos sobre las Micobacterias Atípicas

Cuatro cepas de micobacterias fotocromógenas produjeron enfermedad en los ratones al ser inoculadas endovenosamente. La cicloserina y la amitiozona no produjeron virtualmente el menor efecto sobre la infección producida por esas cuatro cepas. La estreptomicina y la tiocarbanilida (SU 1906) ejercieron efecto limitado contra dos de las cepas, mientras que la isoniacida y la tiocarbanidina (Y 9525) mostraron eficacia mediana contra una cepa y buena contra otras dos. Una de las cepas se mostró absolutamente refractaria a todas las drogas. Los ratones infectados con una cepa resistente a la estreptomicina y la isoniacida no respondieron a la terapéutica al ser tratados con la droga a la cual el microbio era re-

sistente. Las microbacterias atípicas, lo mismo que los bacilos tuberculosos humanos, al ser cultivadas en presencia de concentraciones subinhibidoras de una droga, pierden su farmacosensibilidad.

Resume

Effet in vitro et in vivo des agents antimicrobiens sur les mycobactéries atypiques

Quatre souches de mycobactéries photochromogéniques produisaient la maladie chez les souris inoculées par voie intraveineuse. La cyclosérine et l'amithiozone n'avaient virtuellement aucun effet lorsque l'infection était produite par toutes ces quatre souches. La streptomycine et la thiocarbanilide (SU 1906) n'avaient qu'un effet limité sur deux des espèces, l'isoniazide et la thiocarbanidine (Y 9525) n'exercaient qu'un effet relativement modéré sur l'une tandis qu'elles avaient un effet satisfaisant sur les deux autres. Une des souches était complétement réfractaire à toutes les drogues. Les souris inoculées avec une souche résistante à la streptomycine et à l'isoniazide n'ont pas répondu à la thérapeutique quand elles ont été traitées avec la drogue pour laquelle les organismes étaient résistants. Les mycobactéries atypiques, de même que les bacilles tuberculeux humains, perdent leur sensibilité à une drogue lorsque leur croissance s'est effectuée en présence de concentrations subinhibitrices de cette drogue.

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Case Reports

SEVERE HYPERSENSITIVITY REACTION TO PARA-AMINOSALICYLIC ACID[1, 2]

Report of Two Cases and Review of the Literature

MARIO DE ALEMQUER

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INTRODUCTION

Untoward effects of para-aminosalicylic acid (PAS) and its salts are manifested in several different clinical forms. Gastrointestinal irritation, alterations in thyroid function, electrolyte disturbances, fever, exanthema, urticaria, asthma, and blood dyscrasias are perhaps the more commonly recognized reactions. Whereas the nature of the functional interference resulting from these reactions may be of great clinical significance, the illness produced is only rarely of severe degree.

Systemic hypersensitivity reactions are infrequent, yet may result in a characteristic clinical picture of alarming severity. The frequent occurrence of cholangiolitic hepatitis in this reaction has been recently emphasized by Hensler and associates (1). It is the purpose of this presentation to describe the clinical picture in greater detail and report two new cases.

CASE REPORTS

Case 1. A 20-year-old, white female student had a left infraclavicular shadow with a small central translucency detected on routine chest fluorography. *M. tuberculosis* var. *hominis* was isolated from gastric contents. The afebrile, asymptomatic, 60-kg. patient was placed on bed rest and chemotherapy on February 13, 1954. The regimen chosen was isoniazid (300 mg. per day), streptomycin (1 gm. every second day), and PAS (12 gm. per day).

On the twentieth day of chemotherapy pruritus of the face and a vague uneasiness were noted which were followed by violent chills during the night. The axillary temperature on the next morning was 40.5°C. All chemotherapeutic agents were stopped. On the third day of the hypersensitivity reaction, a scarlatiniform rash appeared on the face and neck which became generalized in a few hours.

The exanthema continued unchanged for five days when desquamation over the trunk and palms began. The axillary temperature which ranged between 39° and 40.5°C. during the first week of the reaction began a slow descent by lysis on the eighth day. During the reaction the prostrate patient was mute and absolutely immobile.

Multiple blood cultures and serologic examinations for Brucella and Salmonella agglutinins were negative. On the seventh day of the reaction, the leukocyte count was 19,600 with 72 per cent neutrophils, 13 per cent eosinophils, 5 per cent lymphocytes, and 10 per cent

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[2] The original manuscript, submitted to the REVIEW by Dr. Alemquer was a more detailed presentation of the observations described in the present report. Because of space limitation, it was not possible to publish the manuscript as originally submitted. Accordingly, with Dr. Alemquer's permission, the original manuscript was turned over to Dr. Charles A. LeMaistre of the School of Medicine, Emory University, Atlanta, Georgia, for condensation. Both the author of the manuscript and the editor of the REVIEW wish to express their appreciation to Dr. LeMaistre for his very considerable contribution to the publication of this report.—*The Editor*.

monocytes. On the thirteenth day of the reaction, conjunctival jaundice, icteric urine, and acholic stools were observed. The jaundice progressively deepened and the bilirubinemia attained a height of 42 mg. per 100 ml. with a positive direct immediate Van den Bergh reaction. A hard nontender spleen was felt 1 cm. below the left costal border, and a moderately tender liver was felt 3 fingerbreadths below the right costal border. The jaundice persisted for about two months accompanied by a low-grade fever.

Three months after onset of the hypersensitivity reaction, the patient was asymptomatic, with a normal hematologic examination, normal hepatic function tests, and only a small fibrotic residual roentgenographic density. The liver and spleen were not palpated. She was discharged without further chemotherapy. Fourteen months later, October, 1955, the left lobe of the liver was easily palpated and found to have a hard, painless, irregular surface. No clinical, roentgenographic, or laboratory evidence of tuberculous activity was obtained, and hepatic function tests remained within normal limits. Cutaneous tests with 20 per cent dihydrostreptomycin and 5 per cent isoniazid were negative, but 20 per cent sodium PAS produced a papule with confluent vesiculation and erythema about 5 cm. in diameter accompanied by marked pruritus and subsequent pigmentation.[2] Dilutions of sodium PAS up to 1:200 gave similar reactions.

Case 2. A 50-year-old cork handler was started on treatment for cavitary tuberculosis on August 10, 1953, with PAS (12 gm. per day) five days per week, streptomycin (1 gm.) three days per week, and isoniazid (300 mg.) per day. On the fifty-eighth day of chemotherapy, October 7, 1953, malaise and pruritus of the face were noted and were followed the next day by a maculopapular exanthema which appeared over the face and neck and became generalized in a few hours. The exanthema became vesicular with abundant exudation and crust formation, mainly on the face. All medication was stopped on October 9. On October 8, the axillary temperature rose to 40.0°C., remained elevated for one week, then descended by lysis, becoming normal on the twelfth day of the reaction. During the initial phase of the reaction, the patient's physical condition deteriorated rapidly. On the second day, severe circulatory collapse ensued, and the patient was considered moribund. At the end of the first week, supraclavicular, cervical, and inguinal lymphadenitis appeared, and the progressively swelling lymph nodes became very painful. The slightly tender liver margin was felt 1 fingersbreadth below the right costal margin. The severe clinical illness receded slowly, disappearing in about three weeks after onset.

On October 16, the leukocyte count was 10,500 per cu. mm. with 67 per cent neutrophils, 16 per cent eosinophils, 10 per cent lymphocytes, and 7 per cent monocytes. The cephalin flocculation, Takata, and MacLagan reactions were positive during the period of high fever, but within normal limits two months later. Cutaneous tests one month after reaction were positive with dihydrostreptomycin, sodium PAS, and isoniazid. Two attempts to renew isoniazid administration, first with 25 mg., later with 0.1 mg., produced violent reactions with high fever and exanthema. Without chemotherapy, the patient ran a downhill course, with hemoptysis and spread of the disease. After failure of viomycin to interrupt the unfavorable course, isoniazid and streptomycin were again administered, but this time concurrently with cortisone. The cortisone was given in a 300-mg. daily dosage by the intramuscular route initially and was later reduced to 37.5 mg. per day. No untoward reactions or sensitization phenomena occurred until attempts were made to reduce the cortisone dosage further, at which time fever and exanthema appeared. Treatment with isoniazid, streptomycin, and either cortisone or adrenocorticotrophic hormone was continued for one and one-half years, at which time the tuberculosis was considered arrested, and the patient was discharged in October, 1955.

Cutaneous tests performed in October, 1955, revealed strongly positive reactions to sodium PAS (1:500) and negative results with isoniazid and dihydrostreptomycin. Administration of isoniazid and dihydrostreptomycin without steroid protection failed to produce sensitization phenomena. Para-aminosalicylic acid was not administered.

[2] Twenty per cent sodium PAS by cutaneous application causes no reaction in nonsensitized persons (2, 3).

Comment: The initial skin tests were positive for isoniazid, dihydrostreptomycin, and sodium PAS; yet only the hypersensitivity to sodium PAS persisted as measured by skin testing. It is probable that all of the clinical manifestations of hypersensitivity were not due to PAS hypersensitivity; nevertheless, the characteristic clinical picture associated with PAS hypersensitivity, including a tender enlarged liver, was produced, with the exception of jaundice. It seems likely that the severe reaction was due in large part to PAS sensitization.

Discussion

Severe hypersensitivity reactions to PAS are infrequent, yet result in a characteristic clinical picture. The reaction usually appears between the tenth and thirtieth days of oral or parenteral PAS administration. The onset may occur earlier than the tenth day in patients who have had previous courses of PAS (4) or may be delayed (as in one of the present cases) considerably longer than one month (5*a*, *b*). The sexes are equally affected, and no age predilection has been recognized. It is perhaps noteworthy that in only one report was the patient a Negro (6). The reaction is heralded by the sudden onset of fever, chills, exanthema, and severe malaise, occurring singly or in combination, with a striking increase in severity of illness in the first forty-eight to seventy-two hours (7). The fever is frequently remittent and reaches a maximum on the second or third day. The pruritic skin rash begins on the face and trunk and spreads rapidly over the entire skin surface. Mucosal involvement is rare. The eruption may be maculopapular, morbilliform, scarlatiniform, urticarial, or even vesicular. Healing follows desquamation. Muscular pains, headache, photophobia, and prostration are often marked. Tachycardia, thready pulse, and hypotension are frequently present. One of the more pronounced and troublesome manifestations is the psychic disturbance which ranges from general indifference to confusion and delirium.

Several days after onset, hepatic, hematologic, and lymph node involvement are often prominent. Liver involvement may be limited to right hypochondrial tenderness and abnormalities in the hepatic function tests; more often there is distinct hepatosplenomegaly and jaundice, sometimes followed by acute yellow atrophy and death. The leukocytosis is usually about 30,000 cells per cu.mm.[3] (8*a*). Eosinophilia from 10 to 40 per cent is frequently present as are atypical lymphocytes simulating those seen in infectious mononucleosis. Lymphadenopathy, especially of the cervical, axillary, and inguinal chains with slight tenderness further simulate the clinical picture of infectious mononucleosis (9*a*, *b*, *c*). Several reviews of pertinent literature are available for more detailed consideration of the clinical manifestations (10*a*, *b*, *c*).

Upon cessation of PAS administration, the reaction subsides slowly over a period of about two weeks. Continuation or renewal of PAS administration leads to recrudescence of the reaction and even to death.

The above description presents the clinical picture most frequently described (4, 5*b*, 6, 8, 9). Variations have been reported such as the absence of jaundice (10*a*, *b*), lack of alterations in leukocytes (11), and agranulocytosis in one patient (5*a*). Transient pulmonary infiltrates with fever and eosinophilia have led to the diagnosis of Löffler's syndrome (8*d*, 12). Prominence of neurologic manifestations simulating the Guillain-Barré syndrome has been reported (13). Other confusing clinical presentations of the reaction have been described (14).

Hypersensitivity to PAS is apparently accompanied by sensitization to many drugs taken simultaneously or even later (4, 6, 7*g*, 8, 9*f*, 10*a*, 15). Part of the clinical syndrome may be produced by the administration of drugs other than PAS, e.g., streptomycin (6),

isoniazid (8*d*), in one of the above reported cases. The complete clinical picture, high fever, exanthema, severe acute illness involving circulatory collapse and/or psychic disturbances, jaundice, lymphadenopathy, and blood dyscrasias, is, however, always a consequence of PAS hypersensitivity. The cutaneous tests further support the hypothesis that PAS itself and not impurities is the primary sensitizing factor in such instances (8*a*, 16).

Early recognition of PAS hypersensitivity reactions is exceedingly important. All patients with fatal disease reported as of this writing had been continued on PAS administration for several days after onset or had PAS administration reinstituted (6, 14*b*, 17). Withdrawal of the drug is the first step in treatment. Desensitization (7*a*, 18) has been successful but not widely used. Antihistaminic therapy has proved of little value, and steroid protection has not been as successful in some instances (8*d*, 9*f*; 10*a*) as it has been in others. Experience is unfortunately too limited for assay of the value of steroids in the management of the PAS hypersensitivity reaction.

Summary

The characteristic clinical picture in the severe hypersensitivity reaction to PAS is described in 2 new cases and the medical literature is reviewed. The six cardinal manifestations of the reaction are high fever, exanthema, appearance of a severe acute illness (circulatory collapse and/or psychic disturbances), jaundice, polyadenopathy, and hematologic derangements.

Sumario

Grave Reacción de Hipersensibilidad al PAS: Presentación de Dos Casos y Repaso de la Literatura

Descríbese en 2 casos nuevos el típico cuadro clínico de la grave reacción de hipersensibilidad al PAS, repasándose a la vez la literatura médica pertinente. Las seis manifestaciones cardinales de la reacción son hipertermia, exantema, aparición de grave enfermedad aguda (colapso circulatorio y/o trastornos psíquicos), ictericia, poliadenopatía y perturbaciones hematológicas. Recálcase la importancia del diagnóstico temprano y de la asistencia apropiada.

Resume

Grave réaction d'hypersensibilité au PAS: Rapport sur deux cas et analyse de la littérature

L'image clinique caractéristique d'une réaction d'hypersensibilité sévère au PAS est décrite dans 2 nouveaux cas, et la littérature médicale est passée en revue. Les six manifestations cardinales de la réaction sont: la fièvre élevée, l'exanthème, les signes d'une maladie aiguë sévère (collapsus circulatoire ou troubles psychiques ou les deux), l'ictère, la polyadénopathie et les désordres hématologiques. L'accent est mis sur l'importance d'un diagnostic précoce avec traitement approprié.

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PULMONARY LYMPHOSARCOMA WITH ALVEOLAR-CAPILLARY BLOCK AND ASSOCIATED COCCIDIOIDOMYCOSIS[1]

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(Received for publication March 24, 1958)

Diseases causing miliary nodular or diffuse reticulated shadows in the chest roentgenogram often present interesting diagnostic problems.

The following case of widespread lymphosarcoma is reported because it caused the "alveolar-capillary block" syndrome and because ante-mortem lung biopsy revealed an entirely different disease, namely, coccidioidomycosis.

Case Report

A 48-year-old white male storekeeper developed sore throat, conjunctivitis, urethritis, and a painful hip in September, 1956. In January, 1957, he complained of productive cough. A chest roentgenogram was obtained (figure 1). Old Tuberculin, 1:1,000, and coccidioidin skin tests were negative; a histoplasmin test was positive. Bilateral scalene node biopsies and a sternal marrow examination were reported to be normal. Fever, chills, and weight loss occurred, and prednisone was administered, with symptomatic improvement. The patient continued taking 5 to 15 mg. of prednisone daily. He moved to Arizona in June, 1957, and one month later to Colorado. Again he suffered daily fever up to 104°F., productive cough, right chest pain, further weight loss, and moderate exertional dyspnea. He was admitted to Colorado General Hospital in August, 1957. Questioning revealed that he had broken many fluorescent bulbs between 1950 and 1955. He denied orthopnea, nocturnal dyspnea, and edema.

Examination disclosed a thin, active male who was slightly dyspneic while talking. Blood pressure, pulse, and temperature were normal. Two small gray areas were present on the uvula and soft palate. No lymphadenopathy was noted. Coarse inspiratory rales were heard in the right axilla. The heart was normal on examination. The liver edge was felt 4 cm. below the right costal margin; the spleen was not palpable. Clubbing and cyanosis were absent. A neurologic examination was unremarkable.

An admission chest roentgenogram is shown in figure 2 and a more detailed film in figure 3.

Laboratory studies revealed a slight anemia and a normal leukocyte count. The sedimentation rate was 38 mm. per hour; a serologic test for syphilis (VDRL) was negative. Serum albumin was 3.4 and globulin 3.9 gm. per 100 ml.; thymol turbidity was 21 units; alkaline phosphatase, 11.5 King-Armstrong units. All other liver function tests, as well as urinalyses and electrocardiograms, were normal.

On microscopy, sputum showed no acid-fast bacilli. Cultures grew a mixed flora; fungal cultures were repeatedly positive for *Coccidioides immitis*, but only after lung biopsy had been performed.

Skin tests on admission were positive to histoplasmin, and negative to intermediate PPD and 1:100 coccidioidin. Four weeks later a skin test was strongly positive to 1:100 coccidioidin. Complement-fixation tests for histoplasmosis, coccidioidomycosis, and blastomycosis were negative.

A bone marrow section was interpreted as showing moderate lymphatic metaplasia; a liver biopsy specimen indicated diffuse subacute inflammation; and a palate biopsy, chronic inflammation.

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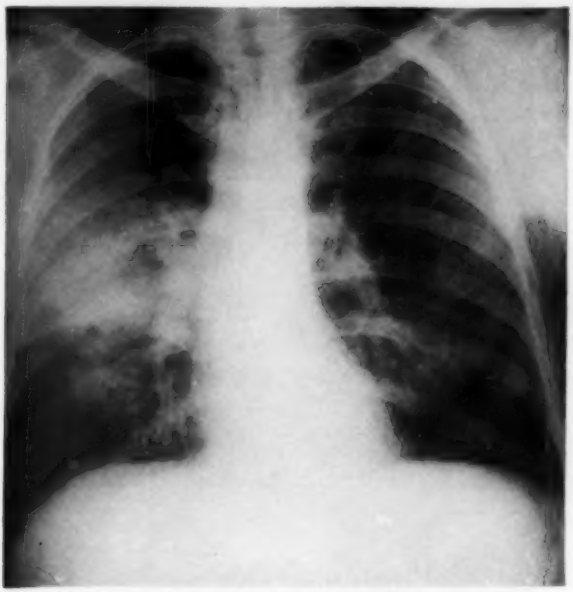

FIG. 1. Roentgenogram taken January 12, 1957, showing diffuse reticulated shadows, as well as confluent densities in the right lung.

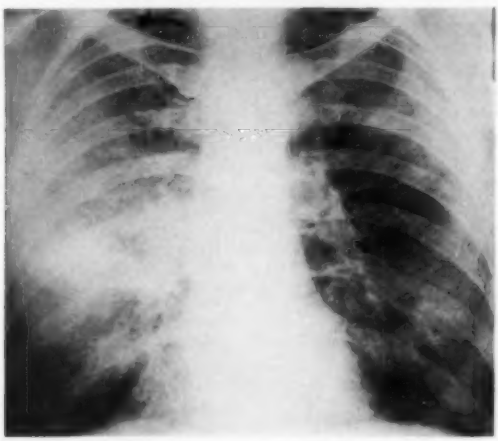

FIG. 2. Roentgenogram taken in August, 1957, showing an accentuation of the pattern seen in January, 1957. Prominent hilar shadows are seen. Tomograms of the right upper lobe revealed a 2.0-cm. cavity.

FIG. 3. Detail view of figure 2 showing miliary nodular shadows and a stringlike reticular pattern.

The following are the results of other tests and diagnostic procedures:

	Actual	*Predicted*
Ventilatory tests		
Maximal breathing capacity	135 L./min.	133
Vital capacity	4,385 cc.	4,000
Maximal mid-expiratory flow	2.33 L./sec.	4.37
Lung volume		
Total volume	5.93 L.	5.30
Residual air	2.91	1.29
Residual/total	49%	24%
Exercise studies (12% grade, 2 miles per hour, 6 minutes)		
Minute ventilation	43.6 L.	
With 100% oxygen	32.6	
Ventilatory equivalent	49.6 L./L. oxygen uptake	
Arterial blood	*Rest*	*Exercise*
Oxygen saturation	90.6%	85.9%
Diffusing capacity carbon monoxide (steady state)		10.5
	5.5 cc./min./mm. of mercury	

A right thoractomy was performed on August 14, and specimens were obtained from the right upper lobe and the apical segment of the lower lobe. The involved segments were indurated, rubbery, and nodular. Microscopically, the specimens showed thick pleura, complete replacement of alveoli by fibrous connective tissue and cellular debris, and heavy infiltration by lymphocytes and plasma cells. Throughout the section were many spherical, doubly refractile organisms containing endospores and resembling *Coccidioides immitis*.

Beginning on August 27 the patient received amphotericin B intravenously for nineteen days, at which time the supply was exhausted. He was discharged on September 18 moderately dyspneic on exertion and with no change in the chest roentgenogram.

Three weeks later the patient was readmitted to the hospital, severely dyspneic and cyanotic. Five days before he had noted chills, generalized aching, increasing cough, and dyspnea. Rales were heard throughout the lungs, and a left pleural friction rub was present. Despite massive doses of antimicrobials and oxygen he died within twenty-four hours.

At autopsy (#57-316) the tracheobronchial mucosa was studded by gray-white nodules up to 2 mm. in diameter. Each lung weighed approximately 1,800 gm., was firm, red-purple, and marked by fine gray granules throughout. Large amounts of fluid were expressed from the surfaces. Areas of soft, friable material were present in the regions of the right lung biopsies. The stomach was 1.5 cm. thick almost in its entirety, and was firm and gray-white. Microscopically, sections of the right upper lobe and right lower lobe showed replacement of lung by nodules of fibrous tissue having necrotic centers with proliferated fibroblasts palisaded about the necrotic portion. The intervening stroma was densely infiltrated by lymphocytes and plasma cells and contained a few recognizable alveolar ducts packed with lipophages and desquamated columnar epithelial cells. The lymphocytes were large and had increased, irregularly clumped, or marginated chromatin. Multinucleated giant cells were scattered throughout. Numerous spherical, endospore-containing organisms with thick, doubly refractile walls were present. Throughout all other lobes, atypical lymphocytes were disposed in nodules around arteries and arterioles and invaded along alveolar septa, or were present in wide bands throughout the parenchyma. The alveoli were filled with neutrocytes and fibrin. The pleura was thickened and infiltrated with atypical lymphocytes. All layers of the bronchi were invaded by these cells. All layers of the stomach wall were diffusely infiltrated by tumor cells, as were portions of the liver, esophagus, kidneys, urinary bladder, bone marrow, and pericardial, peribronchial, and omental lymph nodes.

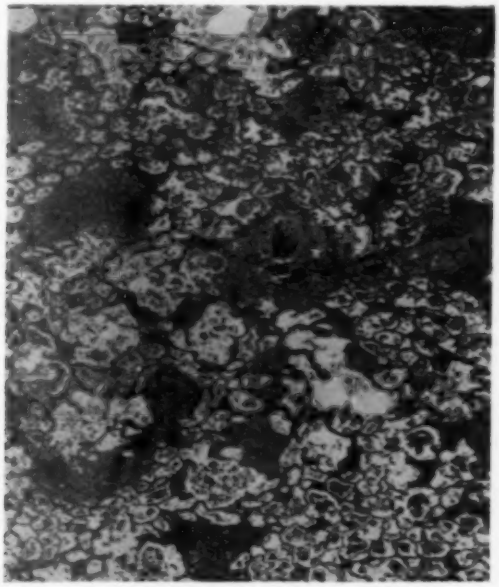

FIG. 4. Section of lung showing diffuse involvement with lymphosarcoma, but without evidence of coccidioidomycosis. Atypical lymphocytes surround blood vessels and infiltrate alveolar septa.

The final diagnosis was lymphocytic lymphosarcoma, coccidioidomycosis of the lung, and bilateral lobar pneumonia.

A representative section of the lung is shown in figure 4.

Discussion

Many chronic diseases may be associated with miliary nodular or diffuse reticular shadows on the chest roentgenogram (1). These include: infections–tuberculosis, histoplasmosis, coccidioidomycosis, blastomycosis, schistosomiasis, hydatid disease; pneumoconioses; aspiration of oily substances; blood dyscrasias; neoplastic diseases; and miscellaneous diseases, such as hemosiderosis, sarcoidosis, diffuse interstitial fibrosis, xanthomatoses, and the so-called "collagen diseases."

Miliary lung lesions are rare in coccidioidomycosis except in terminal cases (2, 3). In disseminated disease complement-fixing antibodies are almost always found in high titer (4), whereas the skin test may be negative. The conversion of the skin test and a negative complement-fixation test in this case indicated recent, localized disease (3).

Lung involvement in lymphosarcoma occurs in 12 to 25 per cent of cases (5, 6), but is usually a late and rapidly progressive manifestation (6–8), although exceptions do occur (8). Lymphosarcoma may cause hilar node enlargement, lobar infiltrations, or miliary disease (6, 8). All of the lymphomas can produce similar patterns on the chest roentgenogram, e.g., nodules, infiltrates, large densities, hilar adenopathy, or miliary shadows (6, 8–10). Pleural effusion is common (6, 10) and cavitation, rare (6). When lung involvement (especially diffuse) occurs in lymphosarcoma, cough, blood spitting, dyspnea, cyanosis, and chest pain may occur.

"Miliary" shadows in lymphosarcoma resemble those seen in lymphangitic carcinomatosis of the lungs and can be described as diffuse stringlike formations radiating out from the hilar regions (which are often enlarged) with miliary mottling or fine nodulation scattered throughout the lung fields (11–14).

Lung biopsy is a helpful procedure in undiagnosed diffuse pulmonary disease (15). Had a biopsy been taken outside the area involved with coccidioidomycosis in the present case, the diagnosis of lymphosarcoma undoubtedly would have been made.

Austrian and associates (16) have given the name "alveolar-capillary block" to a syndrome characterized by diffuse, finely dispersed shadows on the chest roentgenogram—histologically by altered alveolar-capillary septa, and physiologically by a reduction in the diffusing capacity of the lungs. The maximal breathing capacity is usually nearly normal. Hyperventilation occurs at rest and exercise. Clinically, progressive dyspnea, cough, and weight loss are common; cyanosis rarely occurs until late. Reported causes of this syndrome include: miliary tuberculosis, beryllium granulomatosis, asbestosis, silicosis, sarcoidosis, scleroderma, diffuse interstitial pulmonary fibrosis, eosinophilic granuloma, chronic disseminated histiocytosis X, lymphangitic carcinomatosis, and acute leukemia.

The presence of diffuse pulmonary lesions, both roentgenographically and histologically, progressive dyspnea and cough, normal maximal breathing capacity, hyperventilation at exercise, and marked impairment of the diffusing capacity of the lungs in the present case fulfill the above criteria for the "alveolar-capillary block" syndrome.

The association of tuberculosis with Hodgkin's disease is well known (17). Histoplasmosis and cryptococcosis as well as other fungal infections have been described as occurring with lymphomas (17). Impaired antibody formation due to lymphoma has been suggested as an underlying factor (18).

Gastric lymphosarcoma and carcinoma are said to cause similar symptoms; epigastric pain is emphasized as an outstanding feature of the former (19). The patient reported herein had no gastrointestinal symptoms.

Summary

A report is presented of a patient with diffuse lung involvement by lymphosarcoma which produced the "alveolar-capillary block" syndrome.

Sumario

Linfosarcoma Pulmonar con Bloqueo Alvéolo-Capilar y Coccidioidomicosis Coexistente

Preséntase la historia clínica de un enfermo de linfosarcoma con invasión pulmonar difusa que produjo un síndrome de "bloqueo alvéolo-capilar."

Resume

Lymphosarcome pulmonaire avec bloc alvéolo-capillaire et coccidioidomycose

L'observation d'un cas de lymphosarcome avec altérations pulmonaires diffuses produisant le syndrome de "bloc alvéolo- capillaire" est présentée.

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Notes

MASSIVE-DOSE ISONIAZID WITH PYRIDOXINE IN CHRONIC PULMONARY TUBERCULOSIS[1]

Chronic cavitary pulmonary tuberculosis, with the persistence of tubercle bacilli in the sputum in spite of long-term antimicrobial therapy and excellent sanatorium care, is a constant and disturbing problem. Indications[2] that larger-dose isoniazid therapy may be more effective, and the suggestion[3] that the addition of pyridoxine may prevent toxicity, stimulated interest in treating such patients with massive-dose isoniazid in association with pyridoxine.

The study group was composed of 34 patients from twenty-five to seventy-nine years of age. Thirteen of the patients were women and 21 were men; 3 of the women and 5 of the men were Negroes. The length of disease varied from two to fourteen years. With 4 exceptions, all of the patients had persistent cavity and tubercle bacilli in the sputum despite therapy with streptomycin, PAS, and isoniazid for more than twelve months. The patients with the longer histories had received viomycin, cycloserine,[4] and cyanacethydrazide,[5] an analogue of isoniazid that was investigated on this service two years ago. The purpose of the study was to determine the feasibility of large-dose isoniazid therapy: its effect on chronic disease, and the occurrence of drug toxicity when the isoniazid was accompanied by small doses of pyridoxine.

The patients were given tablets containing 100 mg. of isoniazid combined with 5 mg. of pyridoxine (B_6).[6] To facilitate ease of administration, this was later changed to tablets containing 200 mg. of isoniazid with 10 mg. of pyridoxine. The daily dosage used was 20 mg. of isoniazid per kg. of body weight, thus supplying 1 mg. of pyridoxine per kg. of body weight. The administration of streptomycin and PAS was continued.

Leading questions were avoided and, indeed, were unnecessary. The patients freely volunteered subjective feelings, and were closely observed by the nursing staff, resident physicians, and visiting staff. Routine laboratory studies, including hemograms, urinalyses, and liver function studies, were done periodically. Sputum smears, cultures, drug-susceptibility studies, and guinea pig inoculations were performed. Pneumoperitoneum was maintained and surgery was done when indicated. The regular sanatorium regimen of one multivitamin tablet three times daily and 100 mg. of ascorbic acid three times daily was maintained. The multivitamin tablet contained 0.5 mg. of B_6. Thus, a patient weighing 60 kg. received daily 1,200 mg. of isoniazid and 60 mg. of B_6 plus an additional 1.5 mg. of B_6 in the multivitamin tablet.

Twenty-nine patients have received to date six months of therapy. Fifteen patients of this group have completed ten months of treatment and remain under observation. In 5 patients the isoniazid was discontinued because of toxicity. Six other patients who

[1] Presented at the annual meeting of the Eastern Section of the American Trudeau Society, Atlantic City, New Jersey, October 19, 1957.

[2] Hughes, H. B., *et al.*: Tr. Fourteenth Conference on Chemotherapy of Tuberculosis, V.A.-Army Navy, 1955, *14*, 217.

[3] Biehl, J. P. and Vilter, R. W.: J.A.M.A., 1954, *156*, 1549.

[4] Kirshner, J. J.: Dis. Chest, 1957, *32*, 413.

[5] Kirshner, J. J.: in *Antibiotics Annual*, 1957–1958, Medical Encyclopedia, Inc., New York, p. 627.

[6] Kindly supplied by J. T. Groel, M. D., Squibb Institute for Medical Research.

received the drug are not included because they left the sanatorium before completing six months of therapy, or because they received less than 20 mg. per kg. of isoniazid. Eight patients who had completed six months of therapy stopped the drug because of discharge from the sanatorium or because they felt that they were not benefiting from treatment.

Toxic effects from the isoniazid were readily apparent clinically and were promptly reported by the patients. All of the patients initially experienced transient tingling of the fingers and toes. Insomnia was common in female patients, while sedation was seen more often in male patients. Giddiness and light-headedness were noted frequently—the patients stated that they felt "up in the air" or "drunk." In 3 patients, these reactions were severe enough to be characterized as "the staggers." Nervousness as a complaint was difficult to assess. As it was a common complaint of the female patients and was more or less present prior to the use of the drug, it was believed that nervousness was not important as an indication of toxicity. Mental confusion occurred in 2 patients. Gastric discomfort with nausea and occasional vomiting was noted in 3 patients. Shortness of breath was a common complaint in the older emphysematous patients.

In most of the patients these symptoms were not too troublesome and, as drug administration was continued, the effects disappeared. In a few patients the dose was decreased with relief of symptoms, and after a week or two the original dose was reinstituted without untoward effect.

The absence of peripheral neuropathy is interesting in view of previous reports of neurotoxicity with large doses of isoniazid,[7] and the suggestion[8] that previous therapy with isoniazid predisposes to neuropathy when larger doses are used. The protective effect of pyridoxine previously noted,[7] was presumably responsible.

The 5 patients who experienced toxic effects severe enough to warrant discontinuing the drug were older patients with cardiovascular or other complications. All had pulmonary emphysema and reported increased shortness of breath. Two older patients were allowed to continue the drug in spite of mild toxic effects, since no objective findings were noted.

There was only one patient who developed peripheral neuropathy and unsteady gait. This was a Negro male of sixty-seven who never volunteered any complaints. During the routine interview, an unsteady gait was noted and, on questioning, the patient stated he had numbness and tingling of the fourth and fifth fingers of both hands. Examination revealed some thickening of the tendons with slight contractures suggesting a beginning Dupuytrens contracture. He originally had been started on 14 (100 mg.) isoniazid tablets daily, and when the larger-dose tablets were received, he continued to get fourteen tablets a day—a total of 2,800 mg. of isoniazid (140 mg. of B_6) daily for a period of about three months. Stopping the drug and adding parenteral B_6 produced amelioration and eventual clearing of the neuropathy.

One other patient, a Negro male of thirty-two who weighed 135 pounds, was given 1,200 mg. of isoniazid in the drug combination. He gained thirty pounds in five months and the dose was increased to 1,800 mg. of isoniazid a day. Surgery (lobectomy and thoracoplasty) was performed, during which the patient's weight decreased to 140 pounds, and he continued to receive a daily dose of 1,800 mg. of isoniazid without untoward effect.

Another patient, a white male of fifty-two, when questioned as to subjective effects of the drug, stated that the only time he felt any untoward effects was on one occasion

[7] Biehl, J. P. and Vilter, R. W.: Proc. Soc. Exper. Biol. & Med., 1954, *85*, 389.

[8] Biehl, J. P. and Nimitz, H. J.: Am. Rev. Tubere., 1954, *70*, 430.

when he took nine tablets (1,800 mg.) at one time. He felt "drunk, up in the air all day." He didn't repeat the experiment, but continued to take 1,600 mg. of isoniazid daily in divided doses without untoward effect.

There was no evidence that large-dose isoniazid therapy produced dermatologic complications. One patient had a nodular eruption on the chest. These were millet seed-sized nodules deep in the skin which disappeared with continued therapy. Difficulty in starting the urinary stream was noted in one patient with prostatism. There was no evidence of increased or troublesome constipation. There were no convulsive episodes, and psychoses did not occur. Hemoptysis did not occur, and there was no increase of blood-spitting in 2 patients in whom it had occurred previously. One patient who received the drug for one month and who was terminally ill died of a massive hemorrhage. It was the belief of the writer that the disease and not the drug was responsible, as the patient had a huge cavity of the type not infrequently associated with exanguinating hemorrhage. No excessive bleeding was seen in 5 surgical patients. There was no alteration of bleeding, and clotting times and blood prothrombin determinations were normal.

Routine laboratory studies showed no abnormalities. There was no drop in erythrocytes or in hemoglobin content. Leukocytosis was not noted, and there was no instance of eosinophilia. Glycosuria was not found, nor was there any effect on fasting blood sugars or urea nitrogen. There was no evidence of hepatic toxicity in liver function studies.

It is remarkable how little the large-dose isoniazid affected these chronically ill patients. There was very little effect on cough and expectoration: a few patients reported increase in cough and expectoration, and a few thought that there was some decrease. Except for 3 patients, there was no weight gain, whereas the sicker patients lost a few pounds; appetite was affected very little; euphoria was not noted. The patients did not feel "pepped up." Nervousness and insomnia were a fairly common complaint of the women. Hyper-reflexia was not consistent. No effect was noted on pulse or blood pressure.

In 2 patients with recent disease who had had no isoniazid before the study, there was marked clinical improvement. Weight gain was prompt and marked. Cough and expectoration disappeared. Roentgenographic examination showed marked clearing, with closure of cavities; tubercle bacilli disappeared from the sputum. In 2 other patients who had received isoniazid in standard dosage for six months prior to getting the large-dose isoniazid, the improvement was less spectacular. However, there was roentgenographic improvement, and tubercle bacilli disappeared from the sputum of both patients. Two long-term patients gained approximately thirty pounds, but showed no roentgenographic changes or reversal of infectiousness.

All patients with chronic disease continued to discharge tubercle bacilli in the sputum. From the drug-susceptibility studies that have been completed, it appears that those patients who excrete drug-susceptible organisms in their sputum in spite of prolonged chemotherapy continue to do so under massive-dose isoniazid therapy.

Guinea pig studies are being carried out and will be reported on later. However, a sampling indicates that the sputum cultures of some patients produce gross lesions in the guinea pig, while others do not. In the few guinea pigs sacrificed, it was noted that all animals became tuberculin positive whether lesions were present or not.

Remarkably little change was seen on the serial roentgenograms. As has been stated, clearing was noted in the 4 patients with exudative disease. It is believed that clearing was no more marked than that usually seen on standard isoniazid therapy in patients with recent disease. Progression of disease did not occur and, since all the patients with chronic disease had organisms in the sputum resistant to streptomycin, PAS, and isoniazid, it is possible that massive-dose isoniazid used with streptomycin and PAS was a factor in

preventing extension of the tuberculous process. There does not appear to be any contraindication to using large-dose isoniazid with pyridoxine in patients with apparently irreversible disease.

In summary: Thirty-four patients with chronic cavitary tuberculosis were given 20 mg. of isoniazid per kg. plus 1 mg. of pyridoxine per kg. daily. Paresthesias were common, but transient. Severe toxicity occurred in 5 older patients. Peripheral neuropathy occurred in one patient who received 40 mg. per kg. (2,800 mg.) daily. There were no toxic effects on the bone marrow, liver, or kidney. Glucose tolerance was not affected. The clinical course of the disease was unaltered. Tubercle bacilli continued to be discharged in the sputum and roentgenographic changes were not noted.

It is concluded that massive-dose isoniazid is of questionable value in tuberculosis that has failed to respond satisfactorily to other chemotherapies including the conventional dosage of isoniazid.

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January 14, 1958

[9] The writer wishes to acknowledge his indebtedness to Miss Betty Kane, Bacteriologist, and to the staff of The Eagleville Sanatorium for their kind assistance in this study.

IVALON SPONGE PLOMBAGE

Between October, 1953, and May, 1956, forty-three extraperiosteal plombage operations were performed on 40 patients at the East Texas Tuberculosis Sanatorium, Tyler, Texas. There were 28 males and 12 females in the series.

The material used for the "plombe" was the Ivalon sponge,[1] which was inserted in the extraperiosteal space in every case.

This series of Ivalon sponge *plombage* cases illustrate a definitive collapse procedure applied to treatment of tuberculosis cases only, and should not be confused with Ivalon sponge *prosthesis*, which is the subject of a future article. In the latter instance, the sponge is placed intrapleurally to serve as a "space filler" after resection.

Follow-up information was obtained on all patients between September, 1957, and February, 1958. Consequently, all were observed for one and one-half to four years after operation.

The following points outline indications for Ivalon sponge plombage:

All patients in this series had cavitary disease. However, results proved that collapse by plombage should not be employed in cavities 4 cm. or larger in size. In a number of these cases, cavities were present that had persisted or showed progressive enlargement despite the absence of tubercle bacilli from the sputum. Resection was the procedure of choice for unilateral disease in this category.

All but 2 patients had bilateral disease.

With extensive bilateral disease in young patients, bilateral plombage was elected. When performed early, the operation preserved function by preventing the scar contraction and overdistention of uninvolved lung frequently seen after a long convalescence, with drug therapy the only treatment. The plombe, here, served the double purpose of collapsing the diseased lung and acting as a space filler.

In bilateral cavitary disease, in which multiple small cavities existed on one side and larger cavities or a destroyed lobe on the opposite side, the side having the small cavities was selected for plombage before, and in preparation for, resection of the major contralateral disease (figure 1).

Patients, usually in the older age group, who had cavitary disease and low pulmonary function because of emphysema, extensive fibrosis, or other complicating factors, were selected for the plombage, provided the disease was minimal in extent and located high in the lung. Thoracoplasty was the operation of choice if the disease was very extensive.

Selected unilateral cases of patients with low pulmonary function were elected for plombage in preparation for an anticipated later resection (similar to a pre-resection thoracoplasty). The extraperiosteally placed sponge makes an ideal space filler. It can be left *in situ* without interfering at all with the technique of performing a resection in the intrapleural space below. A lobe or lung can be mobilized easily and removed by an approach through the sixth, seventh, or even the eighth rib bed without disturbing the plombage.

There were no early infected sponges in this series. Needle aspiration of the sponge was performed in 12 patients at various times four to eighteen months following operation. In every instance, the fluid recovered was sterile.

In two of the forty-three operations, a late infection of the sponge occurred. The first was no fault of either the sponge or the plombage. This particular sponge had been inserted eight months before in preparation for a subsequent resection. A right middle and lower lobectomy was performed without disturbing the plombe. A bronchopleural fistula developed, followed by an empyema, which in turn infected the sponge. The sponge

[1] Ivalon sponge is distributed by Clay-Adams, Incorporated, New York, New York.

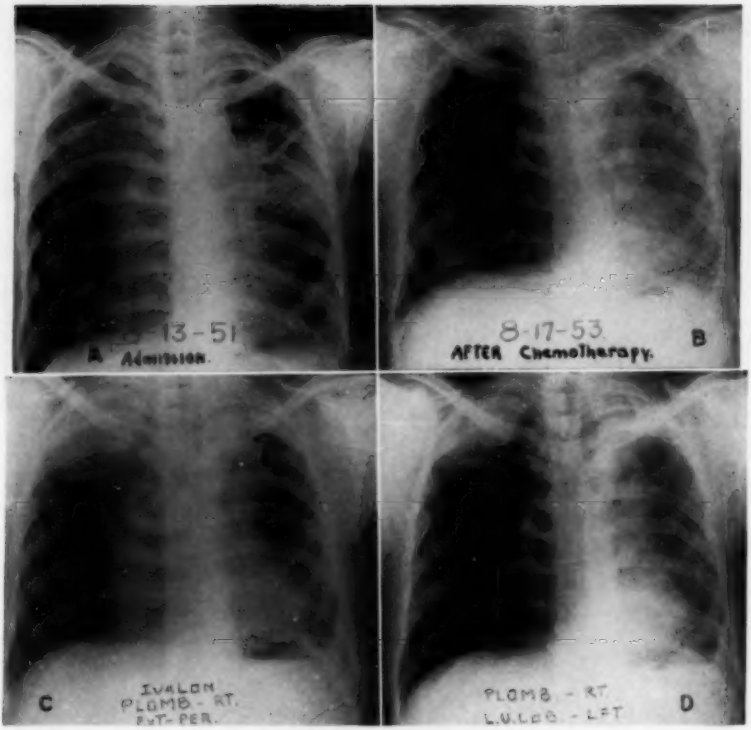


FIG. 1*A*. Film on admission to the hospital. *B*. Film obtained after twenty-four months of chemotherapy, showing a small residual cavity in the right upper lobe and a large cavity in the left upper lobe. *C*. After Ivalon plombage on the right. *D*. After left upper lobectomy.

was removed, the fistula closed, and a concomitant thoracoplasty performed. This patient died ten months later.

The second patient (figure 2) moved to another state, and the infection was discovered by follow-up investigation in December, 1957. It may be mentioned that, in this case, infection was perhaps invited. This patient had had a Lucite ball plombage on the left side in February, 1953. The collapse was insufficient and a cavity remained open. Nearly two years later, in January, 1955, the Lucite balls were removed, the space was enlarged, and an Ivalon sponge was inserted in the same extraperiosteal location. The patient had cavities in the contralateral lung, and was discharging drug-resistant tubercle bacilli in the sputum. Follow-up investigation revealed that the infection apparently occurred about twenty to twenty-four months after operation. The sponge will be removed if the patient's condition permits.

With these two exceptions, no other plombes were removed electively or otherwise.

Effects of the plombage procedure upon pulmonary function were not studied in this group of patients.

Seventeen of the 40 patients had sputum negative for tubercle bacilli before operation.

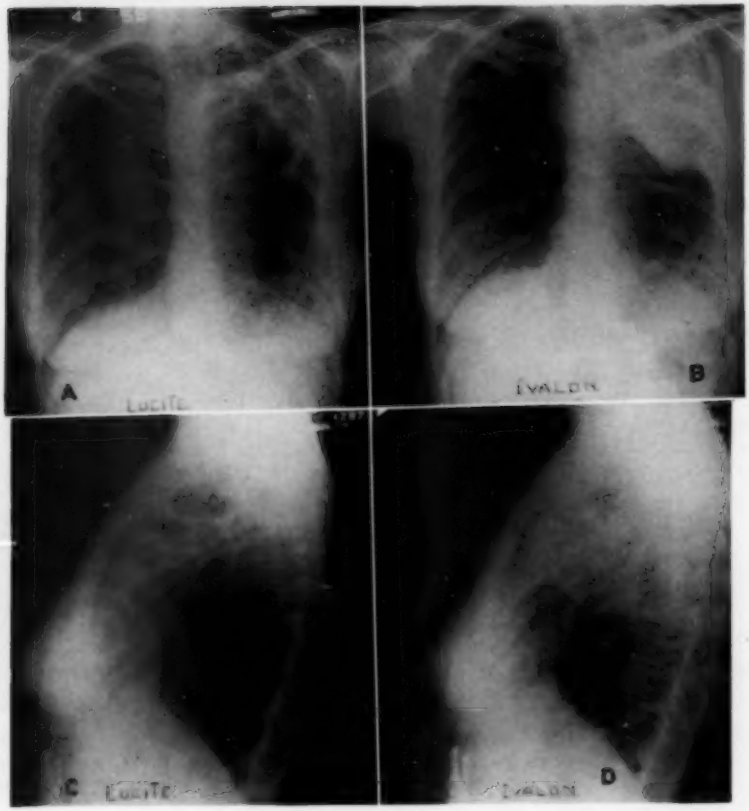


FIG. 2A. Lucite ball plombage on left side. *B*. After removal of Lucite spheres and insertion of Ivalon sponge. *C*. Lateral film showing Lucite spheres and incomplete collapse. *D*. Increased collapse with Ivalon sponge plombage.

TABLE 1

SEVENTEEN "OPEN-NEGATIVE" CASES

Drugs before surgery, 10–45 months, average	24 months
Disease (ipsolateral)	
Large single cavity	4
Small single cavity	3
Multiple cavities	10
Disease (contralateral)	
Cavities	7
Nodular and fibrotic	9
No disease	1

TABLE 2

TWENTY-THREE CASES OF CAVITY WITH INFECTIOUS SPUTUM

Drugs before surgery, 7–48 months, average	25 months
Contralateral disease	
Cavities	11
Nodular and fibrotic	11
No disease	1
Reversal of infectiousness by plombage	11 (47.8%)
Infectious sputum persisted after plombage	12
Residual cavity after plombage	10
Resections below plombage	5
Resections in contralateral lung	3
Died	2
Ultimately infectious status	5
Ultimately noninfectious status (5 after resection)	16 (69.5%)

TABLE 3

TEN GIANT CAVITY CASES (4–5.5 cm.)

Residual cavities after plombage	9 (90%)
Had post-plombage resection (1 died)	4
Died from progression of the disease	1
Refused further surgery	1
Condition would not permit further surgery	1
Future surgery expected	1
Sputum infectious	3
Sputum noninfectious	5 (50%)

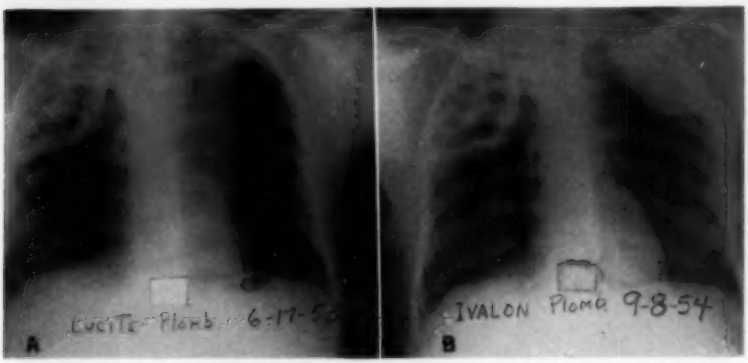


FIG. 3A. Lucite plombage, right. *B*. Two years after Lucite plombage and nine months after Ivalon sponge plombage.

All had multiple-drug therapy for ten to forty-five months prior to surgery. All had open cavities at the time of surgery. Four had large single cavities, 3 had small single cavities, and 10 had multiple cavities on the ipsolateral side. Sixteen of the 17 patients had bilateral disease, 7 with cavities and 9 with nodular and fibrotic disease in the contralateral lung.

One patient had unilateral tuberculosis. One died following a contralateral resection. The remaining 16 patients remain in a noninfectious status, and all cavities, both ipsolateral and contralateral, appear to be closed.

Twenty-three of the 40 patients had tubercle bacilli in the sputum at the time of the plombage. All of the strains of tubercle bacilli were drug resistant, and the patients had had chemotherapy for an average period of twenty-five months. All but one in this group had bilateral disease, 11 had cavities, and 11 had nodular and fibrotic disease in the contralateral lung. In 11 of the group, the sputum became negative for tubercle bacilli following the plombage. Twelve patients remained in the infectious state, and residual cavities were demonstrable under the plombage in 10 patients. It should be noted that 8 of these 10 patients had giant cavities measuring 4 to 5.5 cm. in size. Resections below, without disturbing the sponge, were performed in 5 patients. A sixth patient will have resection in the near future. Resection on the contralateral side was performed on 3 of this group. Two of the 3 deaths in the total series occurred in the group of patients who continued to

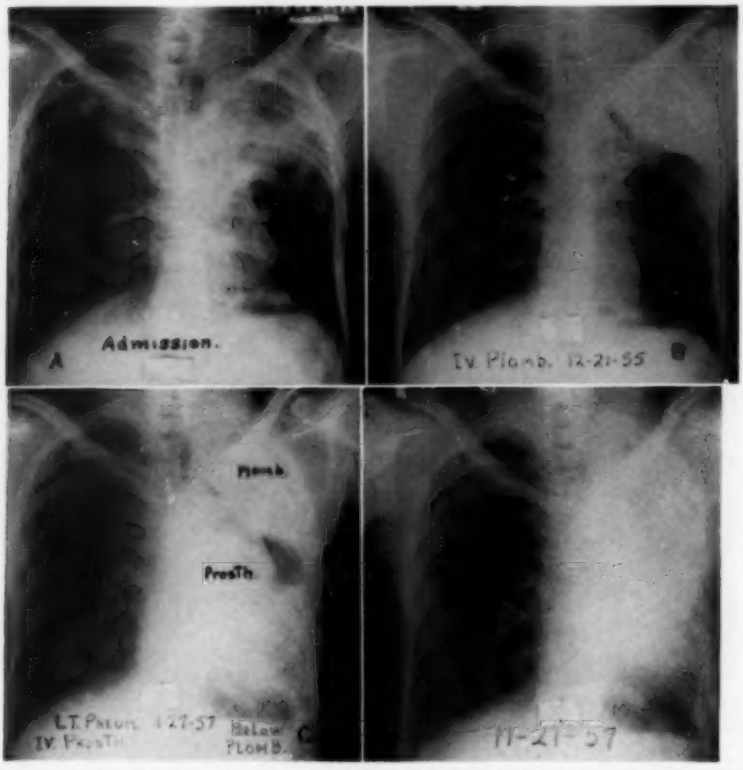


FIG. 4A. Film on admission. *B*. After Ivalon sponge plombage, still showing residual cavities. *C*. Film after total left pneumonectomy showing both the extraperiosteal plombage and the intrapleural prosthesis. *D*. Eleven months after pneumonectomy with both sponges still in place.

discharge tubercle bacilli in the sputum. One died from progression of the disease, and the other, as previously mentioned, had complications following a resection under the sponge. Sixteen of the 23 infectious cases ultimately attained noninfectious status in 5 instances with the aid of resection. Five patients are still discharging tubercle bacilli in the sputum.

There were 10 patients in the total series who had giant cavities, i.e., cavities measuring 4 to 5.5 cm. in size. Nine of the 10 patients still had residual cavities after the plombage and continued to discharge tubercle bacilli in the sputum. The plombage appeared successful in one patient with a 4.5 cm. cavity and noninfectious sputum. Four of this group had post-plombage resections; one, as mentioned before, died. The other 3 patients attained noninfectious status. Of these 10 patients, 5 no longer have tubercle bacilli in the sputum. One other patient is to have a resection, one refused, and one is in too poor condition to permit further surgery.

In the total series, 4 patients had bilateral plombage operations; one of these had a

FIG. 5.4. One month after plombage. *B*. Ten months after plombage. Note: No fluid level and no symptoms. Also, film taken twenty-one months after this film is identical.

TABLE 4

SUMMARY

Plombage operations	43	
Number of patients	40	
Operative deaths	0	
Late deaths	3	
Persistent cavity, noninfectious sputum	17	
Persistent cavity, infectious sputum	23	
Reversal of infectiousness by plombage alone	11	(47.8%)
Reversal of infectiousness aided by resection	5	
Total with reversal of infectiousness	16	(69.5%)
Infectious status persistent	5	
Total patients with cavities	43	
Cavities closed by plombage	33	(76.7%)
Early infected sponges	0	
Late infected sponges	2	

Lucite ball plombage on the right in June, 1953, and an Ivalon sponge on the left in September, 1954 (figure 3).

One patient had an Ivalon sponge inserted on the left side in December, 1955. In January, 1957, a left total pneumonectomy was performed without disturbing the sponge, and an additional Ivalon sponge was inserted within the pleural cavity to act as a prosthesis (figure 4).

There were 3 deaths in the total series. One followed a contralateral resection, one patient died of bronchopleural fistula and empyema after resection under the sponge, and the third died of progression of the disease.

So-called "shrinkage of the sponge" was noted. After a few weeks or months, there was an apparent decrease in size of the plombage averaging one to one and one-half, and in rare instances two, interspaces. This was obviously due to absorption of the bloody exudate and air trapped within and around the sponge, as occurs in the subscapular space after thoracoplasty. In the earlier cases, there was also a fear of consequences from pressure if the sponge was packed too tightly in the space. The technique was changed in the later cases. It is now the practice to pack the sponge snugly so that it will occupy the desired volume of space after fluid absorption. No untoward effects upon the ribs were encountered, and there were no perforations of a cavity by any sponge.

A change in density of the sponge was observed in a few instances, apparently due to absorption of fluid. In none of these instances did the patient present any symptoms such as cough, pain, or fever.

Washing and sterilization of the sponge before use is of the greatest importance. It is thought that some of the unfortunate experiences reported can be explained by improper preparation of the material. Formaldehyde used by the manufacturer for preservation of the sponge must be thoroughly removed before its use. The sponge should be carefully washed a full thirty minutes in running water. It should then be completely immersed in water in a large container and boiled for another thirty minutes or sterilized in the autoclave. Nothing must touch or compress the sponge before it is completely cooled or it will lose its shape. Several such washings and sterilizations will do no harm. After cooling, at the operating table, the sponge can be easily sculptured with scalpel or scissors to fit the space. One million units of penicillin, and one gram of streptomycin in 50 ml. of saline are placed in the sponge at the time of insertion.

In summary: There were no operative deaths and 3 late deaths in forty-three Ivalon sponge plombage operations upon 40 patients (table 4). Seventeen of the cases were the "open-negative" type. In the 23 infectious cases, the plombage succeeded in reversing the infectiousness of the sputum of 11 patients (47.8 per cent). Five others, aided by resection, made a total of 16 reversals of infectiousness in the group (69.5 per cent). All but one of the patients whose sputum became noninfectious by plombage had cavities of less than 3 cm. in size. Thirty-three of a total of forty-three cavities (76.7 per cent) appeared to be mechanically obliterated by the plombage procedure. There were no early and only two late infected sponges in the series. In no instance did the sponge itself seem responsible for any bad result.

4109 Montrose Boulevard
Houston 6, Texas

James E. Dailey

February 21, 1958

Correspondence

TUBERCULOUS MENINGITIS

To the Editor of the American Review of Tuberculosis and Pulmonary Diseases:

Dr. J. Lorber has very properly drawn our attention to a misquotation of his work referred to in the article "Tuberculosis Meningitis" by Nickerson, Morgante, MacDermot and Ross (Am. Rev. Tuberc. 1957, *76*, 832). In table 8 (p. 848), the footnote should have stated that Dr. Lorber found that isoniazid when added to streptomycin and PAS was more efficacious than when streptomycin and PAS were used together. Furthermore, the per cent survival should read 85.5, the correct reference being Brit. M. J., 1956, *1*, 1009, instead of the one given in table 8.

Naturally we are regretful to have given the wrong reference and incorrect figure, which you may be assured was not intentional.

Yours sincerely,
G. H. NICKERSON

ALEXANDRA HOSPITAL
230 CHARRON STREET
POINT ST. CHARLES
MONTREAL, CANADA

May 21, 1958

INDICATIONS FOR ISONIAZID ANTITUBERCULOUS PROPHYLAXIS IN THE COURSE OF NONTUBERCULOUS DISEASE

To the Editor of the American Review of Tuberculosis and Pulmonary Diseases:

The use of isoniazid as a prophylactic agent in tuberculosis has aroused increasing interest in recent years. At the September, 1957, meeting of the scientific committee of "L'Union Internationale contre la Tuberculose" held in Paris, I presented the results of a two-year investigation carried out in experimental animals and in man, and these data have since been published in the *Bulletin de l'Union Internationale contre la Tuberculose*, numero 3–4, 1957. In the December, 1957, number of the AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES, the report of the extensive cooperative investigation of the U. S. Public Health Service was published by Ferebee, Mount, and Anastasiades. This study has to do with the use of isoniazid as a prophylactic agent in children with primary tuberculosis.

In the present communication I would like to raise a somewhat different question than the use of isoniazid prophylactically in persons with a primary infection. The question basically is: "Do particular situations exist today in which adults (or children) with chronic nontuberculous disease should receive isoniazid prophylaxis for the evocation of dormant tuberculous infection which they may have as an incidental finding?" It seems to me that the answer is certainly in the affirmative.

The type of situation mentioned is evident, for example, when it is necessary to treat a patient with one of the chronic rheumatic diseases with an adrenal cortical hormone for a long period. It is well known that today there is a widespread tendency to use such hormone therapy in a number of diseases, such as acute rheumatic fever, rheumatoid arthritis, lupus erythematosus, and many allergic diseases, including bronchial asthma.

By the same token, not infrequently, the evolution of parenchymal pulmonary tuberculosis has been observed in association with such hormone therapy. It has also been shown that corticosteroids are able to worsen the course of experimental tuberculosis in guinea pigs and rabbits. Consequently, we believe that in long-continued corticosteroid therapy, it is essential always to administer isoniazid at the same time. We follow this practice both in patients with detectable pulmonary tuberculous lesions and in the more common situation of persons with tuberculin reactions who show no evidence of pulmonary disease. The regimen we use in this situation is maintained for the entire period of the corticosteroid administration and for at least two months thereafter. The isoniazid is given in a dosage of 4 to 8 mg. per kg. per day.

A somewhat similar situation is presented by diseases producing tuberculin anergy, such as measles, whooping cough, chicken pox, and some of the more severe forms of viral influenza. In my opinion, in these situations it is advisable to give isoniazid in the same dosage (8 mg. per kg. per day) for at least a three-month period during and following the disease.

A different type of situation is presented by the patients who have had gastrectomies because of peptic ulcer. A statistical study carried out by Re and Ferrero of Vercelli on 3,494 cases of progressive pulmonary tuberculosis has revealed the presence of 577 patients who were treated surgically for peptic ulcer. Of these 577 patients, 64 (11 per cent) were affected by tuberculous manifestations which developed into actual clinical disease following the surgery. A similar investigation of 2,273 patients with pulmonary tuberculosis, carried out at the Carlo Forlanini Institute in Rome in 1956, revealed 34 patients who had been subjected to gastric resection and who became infected by tuberculosis following the intervention. It is probable that this phenomenon of post-gastrectomy tuberculosis is partly related to the fact that there has been a marked reduction in infections acquired in childhood and early adult life, with a correspondingly reduced morbidity and mortality. Consequently, there is an increased number of patients without actual pulmonary disease who come to surgical intervention for peptic ulcer. By the same token, a direct relationship between the total gastrectomy and tuberculosis cannot be excluded. It is reasonable to assume that the phenomenon is in some way related to the abrupt changes in the nutritional status of the patients resulting from the surgical procedure.

Because of this apparent relationship between gastrectomy and the subsequent development of pulmonary tuberculosis, it is our practice to administer isoniazid along with vitamin B_6 following surgical intervention. This practice is followed in both patients who previously had pulmonary or extrapulmonary tuberculosis and those whose only evidence of tuberculosis is cutaneous hypersensitivity to tuberculin.

A fourth pathologic situation in which isoniazid prophylaxis is indicated is in pneumoconiosis. The pathologic, anatomic, and clinical relationship between pneumoconiosis and tuberculosis is well known, and today the opinion is held quite generally that silicosis is very often accompanied by tuberculosis. Indeed, some writers state that third-stage silicosis is always a combined form of silicosis and tuberculosis. Apart from these extreme conclusions, most writers agree that the association is present in at least 40 per cent of the patients in second-stage silicosis and in two-thirds, at least, in the third stage.

Silicotuberculosis is nearly always a severe disease, particularly in young adults, and the results of therapy are not always satisfactory even with the most modern methods. In such conditions it is obviously worth while to attempt to prevent tuberculosis evolving during the course of silicosis. I believe that it is possible to do this by administering isoniazid as a prophylactic to all miners with initial forms of pneumoconiosis after suitable

selection by means of clinical and roentgenographic examinations and demonstration of the presence of hypersensitivity to tuberculin. It is our practice to recommend that miners with pneumoconiosis leave work and be treated with isoniazid in a daily dosage of 5 mg. for a period of three months. This cycle can be repeated at three-month intervals for a two-year period, i.e., alternating periods of three months with treatment and three months without treatment.

Finally, I wish to mention the question of chemoprophylaxis of relapse of patients whose tuberculosis has become arrested. In this case, the term prophylaxis is obviously being used quite broadly. It seems highly desirable that any person who has recovered from primary or postprimary tuberculosis should continue to receive therapy for two or three years thereafter; at least in the form of two- or three-month periods of therapy during each of the subsequent years. However, this purpose is seldom reached, either because the patient does not tolerate the drugs, because he forgets to take them, or because the physicians are fearful of giving rise to drug-resistant strains of tubercle bacilli within residual foci. In some special cases, however, such post-treatment "prophylaxis" is advisable because of the relatively high risk of relapse. The patients who are designated as being within this category are as follows: (*1*) women who become pregnant within the period of four or five years following recovery from pulmonary tuberculosis; (*2*) tuberculous patients with diabetes mellitus (for at least a five-year period after arrest of tuberculosis); (*3*) patients with arrested tuberculosis who undergo surgical intervention, particularly gastric and intestinal resections, or repeated vaccinations for diseases other than tuberculosis; patients living in jails or in hospitals for mental disease where the development of epidemic foci of tuberculosis is frequent (G. Daddi); (*4*) patients who have been treated with collapse or excisional therapy for their pulmonary tuberculosis; (*5*) to patients who have recovered from pleurisy or peritonitis, the "prophylaxis" should be administered for at least a five-year period thereafter.

It is probable that, in these situations encountered in the general medical clinic, other indications exist for antituberculous isoniazid prophylaxis than the ones listed above. Nevertheless, the ones listed do represent the principal situations in which this problem arises.

It is possible that the proposals made may give rise to some criticism, but I believe that they have a sound basis in the widespread clinical and experimental experience with isoniazid. This drug is very useful in the therapy of all forms and localizations of tuberculosis and, in our opinion, can be widely used in prophylaxis of new tuberculous manifestations.

Sincerely yours,

A. Omodei Zorini

Carlo Forlanini Institute of I.N.P.S.
University of Rome
Rome, Italy

March 10, 1958

Books

THE SURGICAL MANAGEMENT OF PULMONARY TUBERCULOSIS. No. 1, The John Alexander Monograph Series. Edited by John D. Steele. Pp. 213, Charles C Thomas, Springfield, Illinois, 1957.

This is the first of a series of monographs on thoracic surgery by the students of the late John Alexander. The chapters by individual contributors cover the historical, technical, and chemotherapeutic aspects of the surgical management of tuberculosis. The clarity, brevity, and cohesiveness of the book are unusual for a monograph written by persons of such varied interests. The treatment of tuberculosis has changed so constantly in the past eight years that it would have been quite difficult to write a meaningful and authoritative monograph until the present time. Although the better chemotherapeutic agents of the future will be likely to improve surgical results, the general principles outlined in this book will prove valid for many years. Those concerned with residency training have had no means of describing the problems of the surgery of tuberculosis in the era before chemotherapy. This monograph fulfills this teaching need.

Of particular interest is the chapter on pulmonary resection in the era before chemotherapy. An appreciation of the complications of spread of disease, fistula, and pleural infection is essential to the surgical trainee of today, since operations performed when drug-resistant bacilli are present will result in morbidity similar to that encountered when drug therapy was not available. For this reason, the extensive historical treatment of the subject is of great practical value to the thoracic surgical resident.

Individual chapters review the use of resection, thoracoplasty, plombage, decortication, and cavernostomy. The reviewer was interested to note the remarkable agreement expressed by men who are all leaders in the field of tuberculosis therapy. This unanimity of opinion is perhaps a tribute to the U. S. Public Health Service and the Veterans Administration-Armed Forces cooperative studies, which have been continuously evaluating the results of therapy in recent years. In the face of the statistics gathered in this study, there is little room for disagreement in the evaluation of current methods of therapy as presented in the book.

The monograph is an appropriate tribute to the great surgeon and teacher to whom it is dedicated.

JAMES V. MALONEY, JR.
Los Angeles, California

MODERN DRUG TREATMENT IN TUBERCULOSIS. By J. D. Ross. Pp. 47, National Association for the Prevention of Tuberculosis, London, 1958. Price, 73.6d.

This booklet provides a concise account of conventional drug treatment in tuberculosis. It is very well written and, in a remarkably small number of words, gives all the important facts about these drugs, including clear descriptions of toxic effects and their management.

Dr. Ross has addressed his book mainly to the nurse and health visitor, whose important role in domiciliary treatment he rightly emphasizes. Because so much of the treatment of tuberculosis now takes place in the home, this book would make useful reading for medical students and for doctors in practice.

HAROLD P. LAMBERT
New York, New York

DER LUNGENBOECK IM RÖNTGENBILD. By K. Wurm, H. Reindell, L. Heilmeyer. Pp. 220, Georg Thieme, Stuttgart, 1958. Price, DM 78.

In 1914, the German physician Schaumann published a study in which he postulated that certain characteristic skin lesions, described first by Besnier in 1889 as "lupus pernio" and after careful examination renamed "sarcoidosis" by Boeck in 1899, represented only one manifestation of a systemic disease. This disease was recognized as rare, and led for a great many years an almost small-print existence in European textbooks of medicine. This is reflected in the experience of the reviewer, who remembers having seen only one case during five and a half years of the study of medicine in Germany. The present study, carefully conducted by three renowned clinicians, therefore fills an important gap in the German medical literature. The authors have been able to follow 200 cases of proved sarcoidosis over a period of several years. They give a detailed account of their findings, with special emphasis upon the pulmonary manifestations.

The first part of the book is devoted to general theoretical and clinical considerations. A true increase in the incidence of sarcoidosis in Central Europe has been observed by the authors, who state that its more frequent occurrence cannot be explained solely on the grounds of greater awareness by physicians. In a chapter on pathology, the involvement of the mesenchyme is stressed, and the histologic lesions are described. The crucial points of the clinical diagnosis are discussed in detail, and due reference to the pertinent laboratory tests (serum calcium and protein) is made. In this connection a somewhat more detailed description of the Kveim test would have been desirable. The authors then elaborate on tuberculin reactivity. The percentage of positive reactors in their series of sarcoidosis cases is surprisingly high. Consequently, clinical course and the available methods of treatment are discussed. The authors share the generally held view that the usual benign prognosis makes it difficult to judge properly the therapeutic results obtained with steroid hormones.

The second part of the treatise deals with the problems of roentgenographic diagnosis. Each of the carefully selected pictures is accompanied by a short case history. In the introduction the authors divide the pulmonary manifestations into three stages, the first of which comprises all cases characterized by mere involvement of the mediastinal lymph nodes, while the second one contains the cases showing lymphatic or hematogenous spread. The third stage comprises the fibrotic stage. The following features are considered most important in roentgenographic diagnosis: bilateral, well-defined involvement of the mediastinal lymph nodes, which in the majority of the cases is greater on the right than on the left side, and secondary spread to the tracheobronchial and paratracheal nodes. Two cases illustrate the usually favorable course observed during pregnancy. The chances of spontaneous relapse are discussed and convincingly demonstrated in two other cases. In the concluding chapter, the differential diagnosis is considered. The authors list primary tuberculosis and lymphogranulomatosis as the most important sources of error, while bronchial carcinoma, fungal diseases, silicosis, asbestosis, beryllosis, et cetera can, as a rule, more readily be differentiated from sarcoidosis.

The clear, concentrated style and the well-selected case material make this treatise a valuable source of information for anyone interested in the diagnostic and clinical aspects of sarcoidosis.

DIETHELM BÖHME
New York, New York

Obituaries

Simon Stein Leopold

1892–1958

Simon S. Leopold, a native Philadelphian, lived his life there as a physician and teacher. He will be remembered by generations of students as a constant, wise, and wonderfully kind faculty member at his alma mater, the University of Pennsylvania. He served his internship there and became its Chief Resident.

He interrupted his work for two years when he became a captain in the U. S. A. Medical Corps in 1917. Dr. Leopold was later advanced in academic rank so that he recently became Emeritus Clinical Professor of Medicine; he was in charge of the teaching of physical diagnosis and was chief of the Chest Clinic at the University Hospital for many years.

His book *Principles and Methods of Physical Diagnosis* went into its second edition in March, 1957. He was a thoughtful author of numerous medical reports, and was one of the first to describe massive collapse of the lung. He will also be remembered by a smaller group of students whose lung lesions he helped to locate and treat.

W.H.O., Jr.

Felix Baum

1883–1958

Felix Baum was a native of Germany and a chest specialist who worked in both the eastern and western sections of the United States. He died of a heart attack on January 7, 1958, in South Orange, New Jersey, at the age of seventy-four years.

Dr. Baum studied at Heidelberg and Leipzig universities, and came to America in 1924. He became Medical Director of the National Jewish Hospital in Denver, and a faculty member at the University of Colorado for the next three years. He then entered private practice in New Jersey, first in Newark and then in South Orange. He was the author of several papers on chest diseases. He is survived by his widow, two sons who are both doctors of medicine, a brother, and two sisters.

W.H.O., Jr.

Prescott Archibald Creelman

1895–1957

Dr. Prescott Archibald Creelman was born in Upper Stewioche, Nova Scotia, on August 5, 1895, and died from a coronary thrombosis on April 5, 1957.

He received his medical degree from Dalhousie University in 1925, interned in Grace Hospital, Halifax, and did general practice in Newfoundland in 1925 and 1926. He studied further at Bellevue Hospital, New York City, in 1927, and took a special course in Public Health at Greenville, Ohio. He did special tuberculosis work at River Glade Sanatorium, New Brunswick, in 1927 and 1928.

Most of Dr. Creelman's life following this was spent on Prince Edward Island where he was appointed Provincial Health Officer and Traveling Tuberculosis Diagnostician. During this time a tuberculosis sanatorium was erected in 1931 at Charlottetown. Following its opening, he was made Director of Tuberculosis Control and Superintendent of the Provincial Sanatorium.

Prior to this, he had received commendation for work in tuberculosis control throughout this province, and during his incumbency as Public Health Officer and Sanatorium Director the death rate from tuberculosis fell from 118 to 36 per hundred thousand.

He will be remembered as a great pioneer in public health work on Prince Edward Island.

W.J.B.

Francis P. Dawson

1907–1957

Dr. Francis P. Dawson was born in North Andover and received his medical degree from Tufts Medical School in 1931.

All of his life's work has been devoted to the field of tuberculosis. Following his graduation he was appointed junior physician at Middlesex County Sanitarium, Waltham, advanced to senior physician in 1939, assistant superintendent in 1942, and superintendent in 1946.

Dr. Dawson was considered an authority on community health and tuberculosis and served as instructor in preventive medicine at Tufts Medical School from 1942 to 1948. He also taught at the Harvard Medical School and the Harvard School of Public Health. He served as consultant to the U. S. Public Health Service and also as president of the Massachusetts Trudeau Society and the Middlesex Health Association.

He was a director of the Massachusetts Tuberculosis Health League and member of Delta Omega at Harvard. He had come far in his short life.

W.J.B.

Solomon S. Lubin

1882–1958

Solomon Lubin of New York City died in Chicago in April, 1958, after a long career in tuberculosis work. He had been ill for a long time.

Dr. Lubin was born in Russia. After coming to the United States, he was graduated from New York University and from Bellevue Hospital Medical College in 1913. He interned there, and then had a residency at a sanatorium in Liberty, New York. Dr. Lubin became first physician of the new Deborah Sanatorium and Hospital in New Jersey in 1922, and continued without fee on the staff and board all his life. He had been a consultant to the Jewish "Workmen's Circle" and was on the staff of several Manhattan and Bronx hospitals. He is survived by his wife, three children, and five grandchildren.

W.H.O., Jr.

James Jaso

1891–1957

Doctor James Jaso was born on November 4, 1891, and died on November 6, 1957. He received his preparatory education in Newark, New Jersey, and was graduated from the University of Pennsylvania Medical School in 1920.

He began practice in Newark and was attending physician for workmen during construction of the Holland Tunnel. He became a staff member of Newark City Hospital, now Martland Medical Center, and during this time authored an article on "Silicosis and Primary Carcinoma of the Bronchus."

From 1951–1956 he served as assistant director of the Chest Disease Division, Newark Board of Health. He was a member of the staffs of St. Michael, St. James, and Columbus hospitals in Newark.

Dr. Jaso was a fellow of the American College of Chest Physicians, and a member of the American Medical Association and the Essex County Medical Association.

Dr. Jaso served his community with devotion, distinction, and honor. He is remembered not only by his family but by his friends as well.

W.J.B.

Hiram Burnard Morgan

1905–1957

Doctor Hiram Burnard Morgan was born in Anderson, South Carolina, on August 16, 1905. He received his preparatory work at Furman University, Greenville, South Carolina, and was graduated from the Medical College of South Carolina in Charleston in 1934. He was an intern during his junior and senior years in the Pinehaven Sanatorium in Charleston.

Following his internship he did general practice in Ware Shoals, South Carolina, but continued to be vitally interested in pulmonary tuberculosis and its control as well as all other chest diseases allied to it. He was a member of the South Caroline Trudeau Society and served as president from 1954–1956. He was a member of the American College of Chest Physicians, a member of the Steering Committee which organized the Consecutive Case Conference for the states of Florida, Georgia, and South Carolina. He served on the South Carolina Board of Directors of the Tuberculosis Society from 1939 until 1955, again from 1956 until his death on August 15, 1957, following several years of poor health.

Prior to his death Dr. Morgan served as Director of the Greenwood Tuberculosis Association and Superintendent of Greenwood Hospital. His loss to the community, and to the tuberculosis field especially, is felt by all who knew him.

W.J.B.

Peter Milton Mattill

1887–1957

Peter M. Mattill, long identified with Glen Lake Sanatorium of Minnesota, died at the age of seventy years.

Dr. Mattill was born in O'Daniel, Texas. He was graduated from Rush Medical College in 1919, interned at Presbyterian Hospital in Chicago, and served a residency at Children's Memorial Hospital. Dr. Mattill joined the Glen Lake staff in 1924 after a few years of general practice in Hibbing and Chisholm, Minnesota. During his constant work on the staff, ending as associate medical director and assistant superintendent, he taught for years in the University of Minnesota schools of medicine and nursing. He was a Fellow of the American College of Physicians, a diplomate of the American Board of Internal Medicine, President of the Minnesota Trudeau Society in 1953, and member and officer of many other regional medical and community groups. Dr. Mattill is survived by his wife and four daughters.

W.H.O., Jr.

Armand Laroche

1896–1957

Dr. Armand Laroche died at the Kerbs Memorial Hospital, St. Albans, Vermont on July 6, 1957. He was born in Warwick, Quebec, in December, 1896.

He received his M.D. degree from the University of Montreal Medical School in 1922. Following his internship he settled in a suburb of Montreal where he practiced until 1927. Following a recurrence of an old pulmonary condition he was forced to give up the strenuous activity of general practice.

Dr. Laroche joined the staff of the state sanatorium in Vermont where he served as assistant physician and assistant superintendent for more than thirty years. He was beloved by all of the patients and the employees of the sanatorium.

He was a great reader of medicine, but his interests were not confined to the medical field alone. He loved the outdoors and was interested in landscaping. He also loved to fish, and in later years became interested in square-dancing.

Although burdened by a reactivation of his disease, he gave liberally of himself. This no doubt overtaxed his strength and precipitated his final illness. His philosophy would not have had it otherwise.

W.J.B.

Ethel Byrne

1895–1957

Dr. Ethel Byrne was born in Australia, daughter of a country schoolmaster who raised six daughters who became nurses, teachers, and one, a physician. She graduated from the University of Sydney Faculty of Medicine in 1918, was a resident at Newcastle Hospital, and specialized in pathology. She was honorary pathologist for twenty years, but thirty years ago she began to take an interest in chest diseases which progressed to the point where she became director of the chest clinic. She continued this to the time of her death.

Dr. Byrne was sent to visit chest clinics in Canada, the United States, Great Britain, and Europe in 1955. She was said by her biographers to be wise, kindly, dedicated, gentle, charming, and unselfish. Any one of these qualities would be worth having, or left as a memory.

W.H.O., Jr.

Perry McGregor Knox

1895–1957

Dr. Perry Knox was a native of Pinehurst, Nova Scotia. His education was interrupted by World War I, when he served in the Canadian artillery. He was then graduated from Dalhousie University School of Medicine in 1925, interned at St. John Hospital, and took training in tuberculosis work there. He became Medical Superintendent of Jordan Memorial Hospital in New Brunswick in 1930, and took a similar position at Moncton Tuberculosis Hospital in 1946.

Dr. Knox was a member of numerous medical and community societies. He was certified by the Royal College of Physicians and Surgeons of Canada, and was made an honorary life member of the Canadian Tuberculosis Association. He is survived by his wife and a son.

W.H.O., Jr.

Bret Ratner

1893–1957

Dr. Bret Ratner was noted for his studies of the connections between the fields of allergy and chest diseases. He died suddenly of a coronary thrombosis in New York on October 11, 1957.

Dr. Ratner received his M.D. from New York University College of Medicine in 1918, and served as intern and assistant pathologist on the City Hospital staff. He took further training at the New York Nursery and Child's Hospital, and became dedicated to study and care of allergic children. He worked with Drs. O. M. Schloss and Hans Zinsser, and continued his research, teaching, and practice for almost thirty years, first at New York University and then at New York College.

He was director of pediatrics at Sea View Hospital for Tuberculosis in 1949, and also at the Flower and Fifth Avenue hospitals in 1949.

Dr. Ratner wrote more than a hundred papers and parts of several books. He wrote about children of tuberculous mothers and the use of isoniazid in tuberculous meningitis of children. His list of memberships and honors is too long to list here, but it extended from his college days through recent national and international fields. His progress was the result of hard work, imagination, and the common touch with his colleagues and students.

W.H.O., Jr.

Henry Clemens-Meyer

1908–1958

Dr. Henry Clemens-Meyer was born in Copenhagen, Denmark, took a degree in philosophy in 1927, received his M.D. from the University of Copenhagen in 1936, and lived an amazingly versatile career during his fifty years. He served in several hospitals in his home city for a period of seven years and was chief surgeon in several German concentration camps between 1943 and 1945. Dr. Clemens-Meyer served in the U.N.N.R.A. and British Colonial Services for three years and was associated with the tuberculosis section of the World Health Organization in Switzerland in 1950. He was a Colonel with the 8th Army in Korea in 1952. He worked for a year or two each in Southwest Florida, East Texas, Fort Stanton, and Mount Morris Tuberculosis hospitals, and, since February 1956, has been a Lt. Colonel in the U.S. Army Reserve.

Dr. Clemens-Meyer was a member of several Danish and American medical and chest disease societies. He was decorated by the Danish King with the D.R.K.T. award in 1946. He is survived by his wife, who is on the nursing staff of a Buffalo, New York, hospital.

W.H.O., Jr.

Otto Düggeli

1911–1957

Dr. Otto Düggeli of Davos, Switzerland, died from an unexpected and painful heart attack on December 3, 1957.

Dr. Düggeli was the son of Dr. Max Düggeli, a professor of bacteriology in Zurich. He studied natural science in the schools there, assisted Professor Mollendorf in anatomy at Zurich University, where he became a Ph.D., and an M.D. in 1939, after studies at Zurich, Berlin, and Paris.

Dr. Düggeli then developed serious pulmonary tuberculosis and, after effective therapy

at Leysin, he specialized in the subject with Drs. Steiner of Leysin, Stöcklin of Davos, Gsell of St. Gall, and Rossier in Zurich. He became medical director of the 200-bed Wolfgang Sanatorium at Davos in 1945, and continued a successful career in that position, and was as well a lecturer, a leader in clinical research, and a participant in community affairs. He was a collector of paintings, carvings, stamps, among other things. He is survived by his wife and four sons.

W.H.O., Jr.

NOTICES

The following dates and locations of the next two annual meetings of the National Tuberculosis Association and the American Trudeau Society have been selected and approved:

1959—Chicago, Illinois—May 24–29

1960—Los Angeles, California—May 15–20

ANNUAL MEETING OF THE AMERICAN TRUDEAU SOCIETY

The Medical Sessions Committee *INVITES SUBMISSION OF PAPERS* on all scientific aspects of tuberculosis and nontuberculous respiratory and cardiopulmonary diseases for presentation at the *1959 annual meeting in Chicago, Illinois, May 25–27.*

Abstracts

1. Abstracts of papers to be offered for presentation should be submitted before January 7, 1959, to the Chairman of the Medical Sessions Committee. *Seven copies* are required for distribution to committee members.

2. Abstracts should be limited to a 300-word summary including important data *and conclusions.* Charts and tables should be attached to aid in the selection of papers. Abstracts selected for presentation at the annual meeting will be published in THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES.

3. The names, academic degrees, titles, and complete addresses of the senior author and co-authors should be included in each abstract.

4. All abstracts will be reviewed by the Medical Sessions Committee. Selection will be largely based on the areas of interest suggested by you and others receiving this invitation.

5. Those wishing to present subjects of a confidential nature from the armed forces or other sources should first clear the material through official channels.

6. Authors will be notified by March 1, 1959, if their papers have been accepted for presentation.

7. Papers presented at the annual meeting must be ORIGINAL contributions NOT PREVIOUSLY PRESENTED OR PUBLISHED. Medical papers presented at the meeting may be submitted to THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES by the author if he so desires.

Suggestions

The Medical Sessions Committee is particularly anxious to build the 1959 program around your special interests. A memorandum suggesting subjects and speakers would be welcome and should be sent to the Chairman by October 15, 1958.

H. WILLIAM HARRIS, M.D. *Chairman*
Medical Sessions Committee
American Trudeau Society
1790 Broadway, New York 19, N. Y.

IMMIGRATION OF CERTAIN ALIENS WITH TUBERCULOSIS

Aliens with tuberculosis who are permitted to immigrate to the United States are now required to go promptly to a hospital for examination and necessary medical care, according to a change in immigration regulations. The individual need not be hospitalized as

an inpatient if the responsible physician determines that outpatient care is adequate. Announcement of this change in immigration requirements was made by the Immigration and Naturalization Service of the Department of Justice and the Public Health Service of the Department of Health, Education, and Welfare. Earlier regulations provided for hospitalization "if required," without stating details on enforcement.

Public Law 85-316 of September 11, 1957, contains a provision effective until June 30, 1959, permitting an immediate family member of an American citizen or of a resident alien to immigrate to this country although afflicted with tuberculosis. Other aliens with this disease are barred from admission.

Before receiving an immigrant visa, the alien must submit a statement from a State, territorial, or local health officer, or from the director or a physician staff member of a hospital recognized by the Public Health Service as an institution for the treatment of tuberculosis, agreeing to supply any treatment and observation required for proper management of the alien's condition, in conformity with accepted local standards of medical practice. This statement must also provide that the United States quarantine station at New York will be furnished a clinical evaluation of the alien, including necessary roentgenograms, and a report of final disposal of the case. In each instance the statement of agreement regarding these services must specify the name and address of the hospital at which the services will be provided, and must stipulate that the alien will be given care on an inpatient or outpatient basis when necessary after his arrival at the hospital.

In applying for his immigrant visa the alien must also submit:

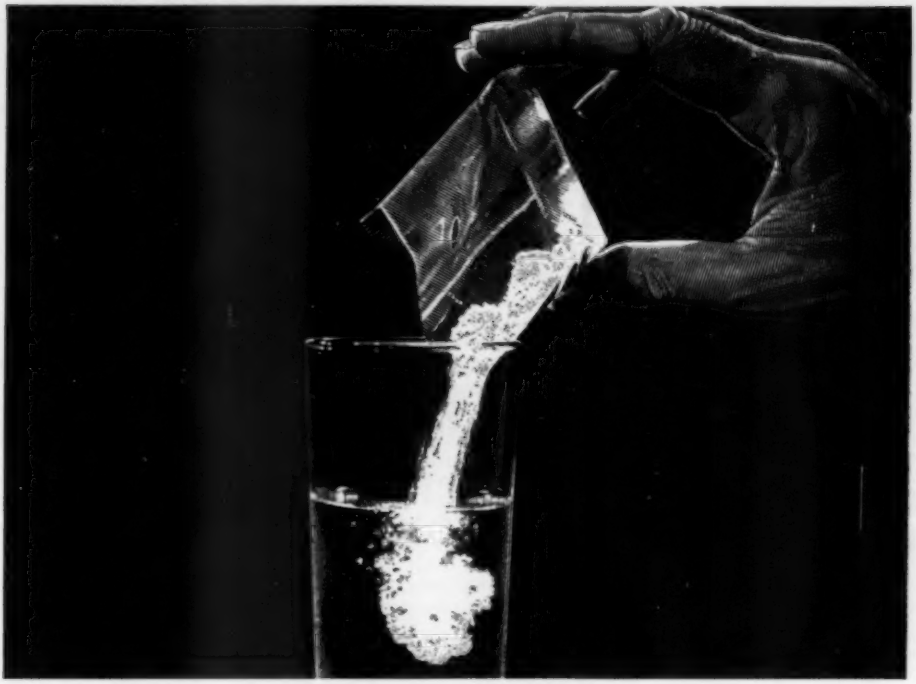
1. An affidavit from a sponsor or other responsible individual that financial arrangements for the alien's care have been made with the hospital, unless the Dependents Medical Care Act applies.

2. Assurance that upon admission into the United States he will go direct to the specified hospital; will submit to such examinations, treatment, isolation, and medical regimen as may be required; and will remain under the prescribed treatment or observation, whether on an inpatient or outpatient basis, until discharged.

3. Assurance that he will comply with the provisions of *Sanitary Measures for Travel of Aliens with Tuberculosis*. This applies only if the alien's tuberculosis is considered to be in communicable form; then he is given a copy of the document.

For purposes of these requirements, the Public Health Service recognizes a hospital as "an institution for the treatment of tuberculosis" if it is listed in *Tuberculosis Beds in Hospitals and Sanatoria*, Public Health Service Publication No. 518. Copies of this have been sent to State health departments and other local health agencies.

The Public Health Service and the Immigration and Naturalization Service have stated that the regulations and controls described above are based on the need for general procedures to ensure that adequate medical examinations and care are provided and that the spread of infection is avoided. Immigration and Public Health Service officials have expressed the hope that, when health departments or qualified private institutions and physicians are called on to provide care for an alien with tuberculosis who is seeking admission to this country, they will carry out the letter of the regulations in order that the spirit of the law may be observed



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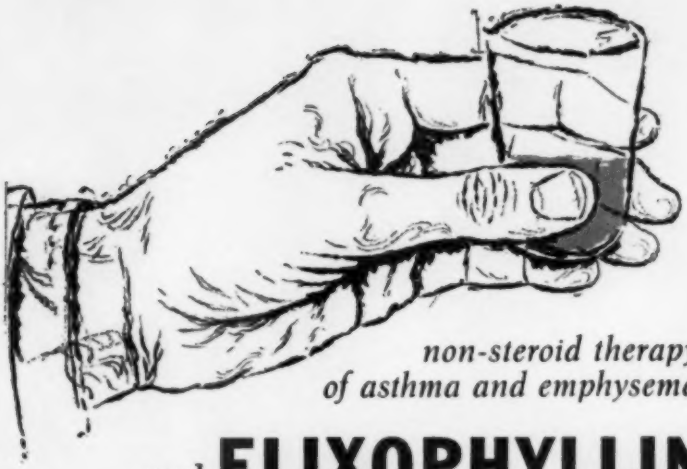

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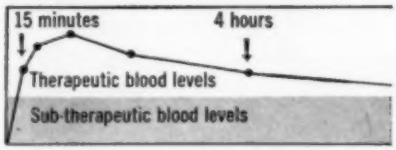

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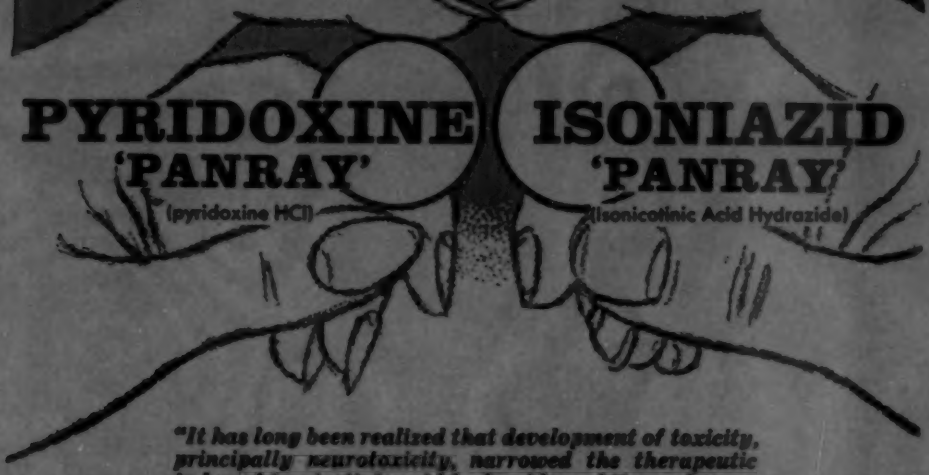

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